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SYMMETRY OF BIOLOGICAL MACROMOLECULES AND THEIR ASSOCIATIONS

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Abstract—The structure of biological macromolecules and their associations obeys the symmetry theory principles. The biological macromolecules are composed of asymmetric small molecules and are found to be chiral. This may be explained by specificity of biochemical reactions. The symmetry groups of biomolecules and their associations have been considered at different hierarchical levels of organization of biostructures—polypeptides, globular proteins, quaternary structure of proteins, viruses, nucleic acids, tubular crystals and ordinary three-dimensional crystals. The data are given on noncrystallographic point symmetry of packing of globular proteins in the crystal lattice, and on the statistics of protein crystal distribution over space groups.

1. GENERAL PRINCIPLES. CHIRALITY OF BIOMOLECULES.

Introduction

The symmetric approach to the analysis of structure of most diverse objects of nature originated in the geometry and aesthetics of the ancients. The theory of symmetry grew out of the study of crystals—their external shape and internal structure. The 20th century brought about the intensive development of this theory, a deep penetration of the ideas of symmetry into many fields of physics, the application of its methods for describing not only geometrical, but also nongeometrical properties of objects[1–3].

Symmetry is also inherent in animate nature—both at a macrolevel of animal and plant organisms and at a microlevel of the structure of biomolecules and their various associations. The development of structural molecular biology involves the use of symmetry principles, elucidation of the causes of symmetry manifestation in the hierarchy of living systems, and gives an impetus to development of the symmetry theory itself.

Symmetry is the invariance, self-equality of objects

A symmetry transformation of a symmetric object changes nothing in it—the object remains equal to itself, invariant to this transformation (Fig. 1). The object—its structure and properties may be depicted by a function $F(x_1, x_2, x_3 \ldots) = F(\mathbf{x})$ in space of the variables used for its description $x_1, x_2, x_3, \ldots = \mathbf{x}$. For geometric symmetry in three-dimensional space $x_1x_2x_3 = \mathbf{x}$ are the Cartesian coordinates. The symmetry operation g^i transforms the coordinates: $g^i(x_1x_2x_3) = x_1^i, x_2^i, x_3^i$; $g^i(\mathbf{x}) = \mathbf{x}^i$. Thus, an object is symmetric, if

$$F(\mathbf{x}) = F(\mathbf{x}_i) \equiv F[g_i(\mathbf{x}_1)]. \tag{1}$$

Mathematically, a set of g_i for a symmetric object makes a *group* $G = G[g_1, \ldots, g_n]$. The operation of identity "immobility" of an object is the unit $g_1 = 1$ of the group.

From (1) it follows that important for symmetry are not the specific function values F at different $\mathbf{x}$, but the regular relationships, i.e. the transformation operations acting on variables $\mathbf{x}$ to which F is invariant—this is the invariability which makes the object symmetric.

Asymmetric unit

The transformation g of an object into itself implies that its parts disposed in one place will be brought into coincidence, after transformation, with the parts located in another place. It means that the object may be divided into equal parts A_i (Fig. 1(b)).

The smallest part of a symmetric object F which, when being multiplied by all the operations g_i of the group G forms the entire object, is called an independent or asymmetric unit—a "stereon" in three-dimensional space. The number of stereons in an object is equal to the group

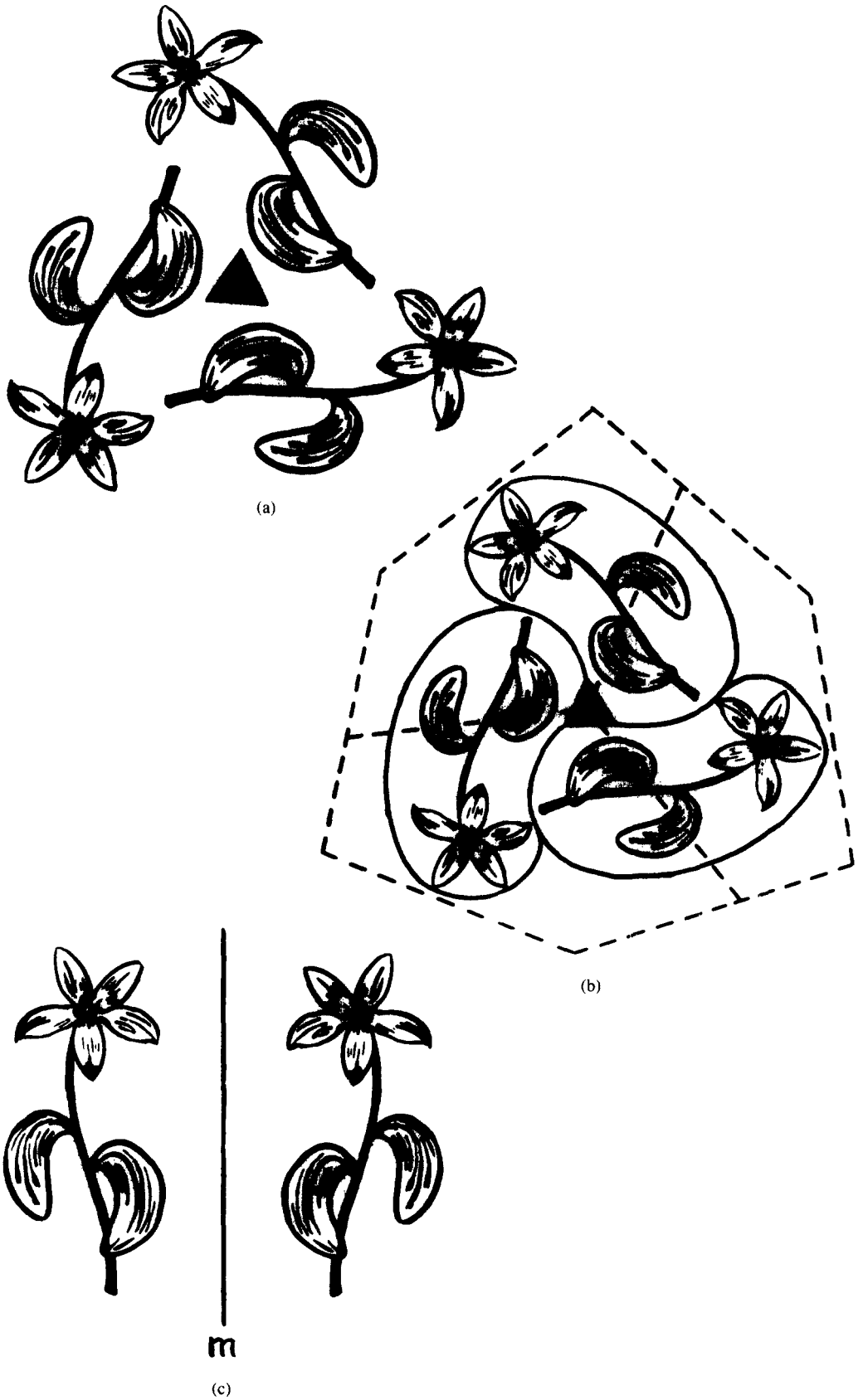


Fig. 1. (a) Symmetric object with the three-fold axis of symmetry; (b) the object may be divided into equal parts—stereons, by the infinite number of ways. Dashed line shows an example of an arbitrary division, solid line—division into "physically isolated" stereons; (c) mirror-equal asymmetric figures.

order n. Each stereon A_i may be obtained from stereon A_1 chosen as the initial one, by "its own" operation g_i:

$$g_i[\mathbf{x}_{(A_1)}] = \mathbf{x}^i_{(A_1)} \quad i = 1, 2, \ldots, n. \tag{2}$$

In nearly all the groups there exists some arbitrariness in the choice of stereon boundaries, i.e. in its shape (Fig. 1(b)); at such a choice only the point symmetry elements of an object—axes, planes and the inversion center—are fixed.

Origin of symmetry in nature

Why does symmetry permeate almost all constructions and laws of animate and inanimate nature? This fundamental question has received no general answer as yet. Mathematicians postulate, axiomatize and analyze various symmetries, physicists find it in ever-increasing number of natural phenomena and make use of predictive power of the group theory, biologists certify primordial asymmetry of small molecules of life holding together in highly symmetric associations. But what is in common in all of this?

Apparently, initial is the concept on a *finite set* of sorts and *equality* of elementary entities of which larger units at a definite matter organization level are composed. At the lowest level these are elementary particles and quarks they are made of, and the fields acting between them which can be represented again as particles of which everything existing is formed. Further, their association into nuclei and atoms leads to a new level of elementary entities whose number is also finite, and whose special aggregations provide a practically infinite set of various objects. Among these objects are molecules and crystals, and the molecules may be used anew to build more complex molecules and their associations.

However, the geometrical equality as such is a necessary, but insufficient condition for the symmetry origin. There must also be the equality in interaction, geometrically, it should be manifested in mutual arrangement of equal parts. Being governed by principles of conservation and thermodynamics, the nature imposes restrictions on the infinite number of interaction modes. It may well be that the principle of energy minimum is the most important one as regards the appearance of symmetry in three-dimensional objects[3].

If the energy minimum has been achieved at a certain configuration of an isolated subsystem, the configuration should be the same for all similar subsystems. One may believe that the energy minimum in a system composed of finite or infinite number of such subsystems is also attained at their symmetric combination with the account for their interaction energy. Otherwise, the inequality of interaction, the inequality of arrangement (when only geometry is taken into account) will cause a difference between the subsystem energies, which would be in conflict with the subsystem energy equality condition. Just in such a way we may explain, in particular, the symmetry of molecules composed of several sorts of identical atoms. If the number of atoms is very large or infinite, this approach allows one to understand the origin of translational symmetry in crystals or in polymer molecules.

As already mentioned (see Fig. 1(b)), the choice of an asymmetric unit—the stereon A of a symmetric object F, is, geometrically, ambiguous. But from the viewpoint of energetic stability or structural isolation, one can often choose a "physical stereon" (Fig. 1(b) solid line). Thus in the case of molecular biostructures it seems physically justified to take, as a stereon, an individual molecule together with some space around it, since the molecule is a firm structural unit: the atoms in it are covalently bound whereas the van der Waals forces between the molecules are weak. The case of asymmetric molecules is especially favourable for "physical" choice of a stereon, although, geometrically, the arbitrariness still remains. It should be noted that such a "physical" choice is not always possible, e.g. when the interaction between "parts" of a system is of the same order as inside these "parts." As an example one may consider the complex inorganic crystals in which a continuous spatial network of approximately equivalent bonds between atoms exists[3].

Pseudosymmetry and morphological symmetry

For some objects the symmetry conditions are not fulfilled precisely. Then, although, approximate, the equality in some parameters describing the system or its parts, enables the

manifestation of symmetry laws. For instance, the molecules, similar in structure, can form pseudosymmetrically packed associations (see Fig. 18 below).

An interesting and important case is the morphological symmetry—the symmetry of an external shape. Human body is symmetric externally, but asymmetric in its internal organs. A symmetry of the form in this, as well as in other cases, is determined by the interaction with the environment. On the contrary, the ideal symmetry of the crystal habit is fully defined by the inner atomic structure of crystals, but the real habit and its symmetry turn out to be dependent on the crystal growth conditions.

The formation of biological structures

A physical approach to elucidate the structural laws of atomic systems and their symmetry is universal and may also be applied to biological macromolecules. However, the biological systems possess their own, specific laws of structural organization which, acting within the framework of general physical laws, modify the manifestation mode of the latter. Moreover, the combination of atoms and small molecules in a macromolecule and the subsequent self-organization into the higher-order structures proceed not as the result of random events of physico-chemical interactions between them, but according to a *compulsory program* stored in the DNA genetic information. As already mentioned, the energy needed to accomplish this program is available.

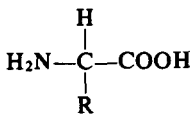
Biological systems possess many very important specific physical features. These systems are *open* thermodynamically and exist in a free energy flow through themselves, this flow being provided by chemical metabolic reactions. The biological systems, according to E. Schrödinger[4], "consume" negative entropy (negentropy) which, contrary to the entropy, a measure of disorder, is a measure of order. This means that a mechanism of ordering is operating within each biological system.

Thus, the biosystems exist to continue their existing, self-reproducing and developing.† We can say that the category of causality permeating the physical laws that realize it in inanimate nature, may be interpreted in biological systems as a category of purposefulness of functioning of all its micro- and macroscopic parts.

What conclusion can be drawn from the above to understand the symmetry of biomolecules and their associations? Symmetry bears in itself the principle of economy of the number of certain main building blocks in the process of biosystem formation and arises where it may be of help. In the conditions of cellular medium the symmetry of macromolecules depends on local physical conditions. Genetic information governing the appearance of macromolecules with a definite chemical structure "takes into account" the conditions in which the macromolecule will exist and through them exerts influence on the arising spatial structure. On the other hand, the structure and symmetry of macromolecules during their interaction with each other in a given medium determine the construction of higher-level associations built of them.

Asymmetry of small living protomolecules

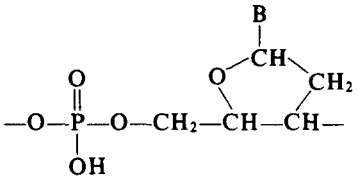
One has to begin the specific consideration of the symmetry of biomolecules with the fact that the small, primary biomolecules—so-called protomolecules of which large molecules and their associations are built, are asymmetric, i.e. devoid of any symmetry: the protomolecules are depicted by the only asymmetric group $G = 1$. Protomolecules are the amino acids of which proteins consist and the nucleotides of which nucleic acids are built. Amino acids



(3)

†We cannot dwell here into mechanisms of the accumulation and transfer of information in biosystems, into the origin and evolution of living systems on the basis of variability and natural selection; this would lead us far away from the topic of this article.

(there are twenty sorts of main amino acids) vary in their side radical R. Nucleotides contain pyrimidine or purine bases B of four sorts: adenine A, thymine T, guamine G, cytosine C (in RNA thymine is replaced by uracil U) attached to a sugar-phosphate backbone



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The carbon atom in an amino acid is surrounded tetrahedrically by four different atoms (atomic groups) and is, with respect to the surroundings, asymmetric (Fig. 2(a)). Ribose of nucleotide also contains asymmetric C atoms.

Symmetry groups of biomolecules and their associations—groups of the first kind

Symmetry operations congruently bringing a figure and its asymmetric parts to coincidence as in Fig. 1(a), are called operations of motion or the first-kind operations g^{I}. These are parallel displacements, rotations and their combinations: screw motions. The corresponding groups are the first-kind groups G^{I}. At the second kind operations g^{II} asymmetric parts of a figure are equal in the general meaning of symmetric equality[1,2], they are mirror-equal (Fig. 1(c)), but no motion can bring these parts to coincidence, i.e. they are not equal congruently, i.e. physically. The groups containing the mirror-equal operations g^{II} and other operations of the type g^{II} arising from them, e.g. the center of inversion, are the groups G^{II}.†

Any asymmetric object or the object depicted by the first-kind group G^{I} may have a mirror-equal figure—enantiomorphic one (Fig. 1(c)). The property of such objects, say, molecules, to exist in two mirror-equal, enantiomorphic forms is called chirality. As for the objects depicted by the groups G^{II}, they are chiral to themselves. Usually, one of the pairs of the chiral objects is called "left-handed," the other "right-handed" by analogy with the right and left hand. The "left," "l," tetrahedral C atom (exactly speaking, surrounded by the left mode), specific for living matter, is shown in Fig. 2(a). Its chiral analog, the "d" C atom that can also be found in biomolecules is shown too.

Thus, all biostructures, i.e. the living matter as a whole, is chiral, because chiral are the protomolecules it is formed of. Chirality of protomolecules does not preclude their joining into the symmetric higher-order structure, but the symmetry of thus obtained associations is only the symmetry of the first kind G^{I}.

The cause of chirality of living molecules is usually assumed to lie in the origin of life, in general, e.g. in chirality of some nonbiological structures, minerals, on which the first

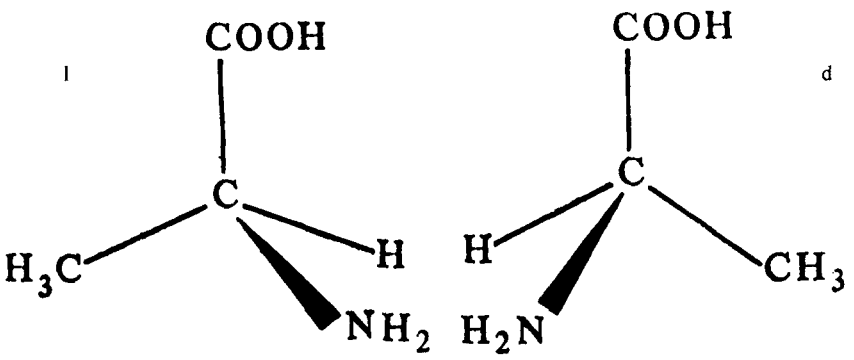


Fig. 2. Left-handed—l, and right-handed—d, alanines.

†The groups G^{II} may contain g^{I} operations, too. No combination of motions, i.e. of operations g^{I} can produce the operation g^{II}, while combinations of even number of g^{II}, give an operation of the type g^{I}.

biological reactions might take place, in polarization of solar radiation[5]. Recently, the ever-increasing development have received the hypotheses connecting the asymmetry of protomolecules with the fundamental physical asymmetry of elementary particles and their interactions, although the manifestation of such interactions at the atomic level in chemical bond between atoms during the molecule formation, is quite negligible.

Apparently, chirality is associated substantially with exceptional specificity of all bioorganic reactions. The right and left molecules (the objects with symmetry G^{I}) are chemically and physically equivalent when interacting with non-chiral objects having the second-kind symmetry G^{II}. But they appear to be different, nonequivalent in interaction with the objects which are chiral themselves, possessing symmetry G^{I}.† If we denote a level of interaction, its specificity, by E (it may be, e.g. the interaction energy, constants of reactions etc.) then

$$E(G^{I,L}_{(1)}, G^{II}_{(2)}) = E(G^{I,R}_{(1)}, G^{II}_{(2)}) \tag{5a}$$

$$E(G^{I,L}_{(1)}, G^{I}_{(2)}) \neq E(G^{I,R}_{(1)}, G^{I}_{(2)}) \tag{5b}$$

$$E(G^{I,L}_{(1)}, G^{I,L}_{(2)}) = E(G^{I,R}_{(1)}, G^{I,R}_{(2)}) \neq \tag{5c}$$

$$E(G^{I,L}_{(1)}, G^{I,R}_{(2)}) = E(G^{I,R}_{(1)}, G^{I,L}_{(2)}) \tag{5d}$$

$$E(G^{II}_{(1)}, G^{II}_{(2)}) = E(G^{II}_{(1)}, G^{II}_{(2)}). \tag{5e}$$

Thus, only in case (5b) which is examplified by variants (5c) and (5d), the interaction proves to be specific. The specificity in the interaction of biosystem molecular components with each other or with the environment contributes to its autonomy, uniqueness of structure and peculiarity of the ways in which some or other reactions proceed in it, and serves as a tool providing protection and selectivity at a contact with chemical substances of the environment.

Condition (5c) in which the terms written on the left and right are "mirror image" of one another shows that the mirror-equal interactions between pairs of the L and R-objects are possible (the same holds true for LR- and RL pairs). Condition (5c) shows that the R-world analogous to our L-world of animate nature is possible. However, according to the main condition (5b) such a world R would be incompatible with the existing world L and vice versa. Also, they could not interact correctly between themselves. Therefore, if at the early stages of the origin of life the L and R (or LR) systems might come into existence, in the competition only one type out of them survived. More unstable, indifferent to reactions not only with the chiral (a), but also with the non-chiral objects would be the world of the type (5e).

Principle of hierarchy and of small number of elements

Living systems are built up according to the hierarchical principle. The first (lowest) steps in this hierarchy are small protomolecules. Important is the fact that there is only a small number of their sorts, but it allows an infinite number of chemical and spatial combinations. The next step is concerned with the individual macromolecules of proteins, nucleic acids and polysuccarides. The number of their sorts is extremely large, but, in structural organization, they form a limited number of types. Out of the unlimited number of combinations of macromolecules the nature prefers the regularly, symmetrically, expediently built associations. The main unit of a living organism, the cell, is asymmetric, although in some of its organella a symmetry can be observed.

2. SYMMETRY OF BIOSYSTEMS AT DIFFERENT LEVELS OF MOLECULAR ORGANIZATION

Symmetry groups of biomolecular systems

The grouping of protomolecules into biomacromolecules and the arrangement of macromolecules into associations can be described by groups of symmetry of three-dimensional space G^3 and only by the first-kind groups $G^{3,I}$[1,3].

†One cannot get the right boot on the left foot, it is merely awkward. Enantiomorphic analogs of useful medicine substances may prove to be indifferent or harmful.

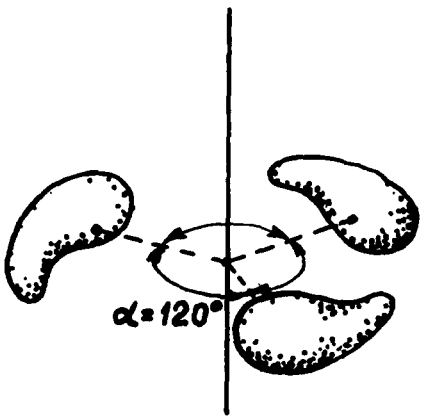
These groups may contain only the following operations and symmetry elements corresponding to them (Fig. 3(a–c)):

Rotations N around the N-order axes through $2\pi/N$

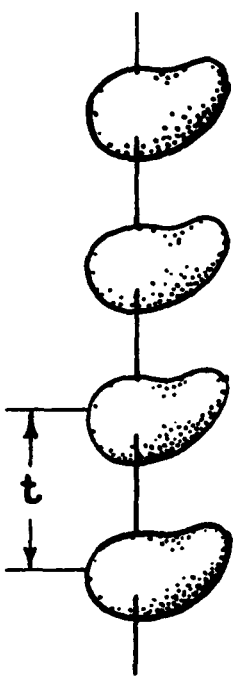
Parallel translations t through the period c

Screw (helical) rotations S_M: combination of a translation along t on $c' = c/M$ with the rotation on $\alpha = 2\pi/M$ around the axis of translation. M: the parameter of a screw rotation may be the integer $M = N$ or fractional: $M = p/q$, p: the number of rotations per q turns,

$$\alpha = 2\pi\frac{p}{q}, \quad c' = \frac{qc}{p}.$$



(a)



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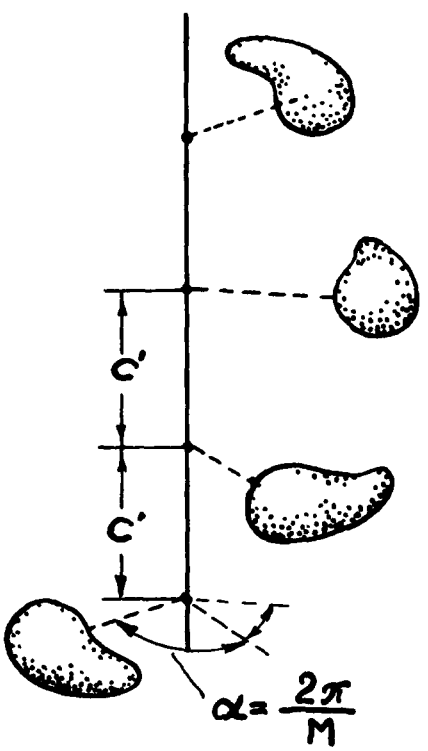


(c)

Fig. 3. Symmetry operations of the first kind: (a) rotation ($N = 3$); (b) translation t; (c) screw rotation S_M.

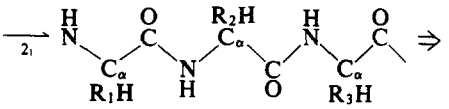
If the number of particles being joined together is finite, such association is described by the point groups $G_0^{3,1}$ containing only rotations. At the infinite number of particles in an association there always takes place periodicity (the lower index in the group notation). The groups G_1^3 with periodicity in one direction depict the chain and helical structures. The twice periodic groups G_2^3 depict layers[3,6]. Triple periodic groups G_3^3 are Fedorov space groups of symmetry of crystals. The characteristics of groups $G_m^{3,1}$ are given in Table 1.

It should be emphasized that the order of rotations N or screw rotations M in biostructures may be any one in all cases, except biocrystals. In crystals, due to the presence of the lattice only simple or screw rotations of order 2, 3, 4 and 6 are possible. In biostructures also the axes of the 5th, 7th and highest orders as well as screw rotations with fractional M are not forbidden.

Let us consider various molecular biostructures. The information on their structure has been, mainly, obtained with the aid of X-ray structure analysis[7].

Peptides, polypeptides

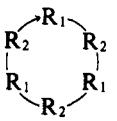
The protomolecules (3) are asymmetric, point group 1. Linking of amino acid residues by peptide bonds gives a chain



(6)

The polypeptide chain is polar, the running NH—C_αRH—CO—⇒ in one direction is different as compared with the running in the opposite direction. The chain has the symmetry $S_2 = 2_1$ (two-fold screw rotation), denoted by →.

Therefore, small peptides of an open chain are always asymmetric (group 1). On the contrary, the cyclic peptides—closed chains and related molecules may have the N-order axis, e.g. the cycle



(we designate the amino acid residue simply by its radical) has the axis of symmetry 3. An example of such a molecule is given in Fig. 4[8]. The combination of two similar rings, lying

Table 1. Symmetry groups $G_m^{3,1}$

Groups	Types of groups	Number of groups	Representatives in biosystems
Point $G_1^{3,1}$	N, $N2$, 3/2, 3/4, 3/5 All symmetry elements intersect at a special point	$N + N2 + 3$ Infinite, depends on order N	Small protomolecules, oligonucleotides, globular proteins, RNA, viruses, nucleoproteids
Chain $G_1^{3,1}$	Nt, $Nt2$, S_MN, S_MN2	Infinite, depends on values N and M	Secondary structure of proteins, fibrous proteins, DNA, tubular crystals, rod-shaped viruses
Layer $G_2^{3,1}$	Combination of $t_1t_2 22_1$, 2	9 (out of the total number G_2^3 80)	Secondary structure of proteins, layered biocrystals, membranes
Crystal $G_3^{3,1}$	Combinations of $t_1t_2t_3$ N = 1, 2, 3, 4, 6 S_M at M = 2, 3, 4, 6	65 (out of the total number of Fedorov space groups 230)	Crystals of proteins, oligonucleotides, viruses

2, 3, 4, 6 are the axes of rotation of the corresponding order, Nt—parallelism N to translation t, $N2$—axes 2 are perpendicular to N.

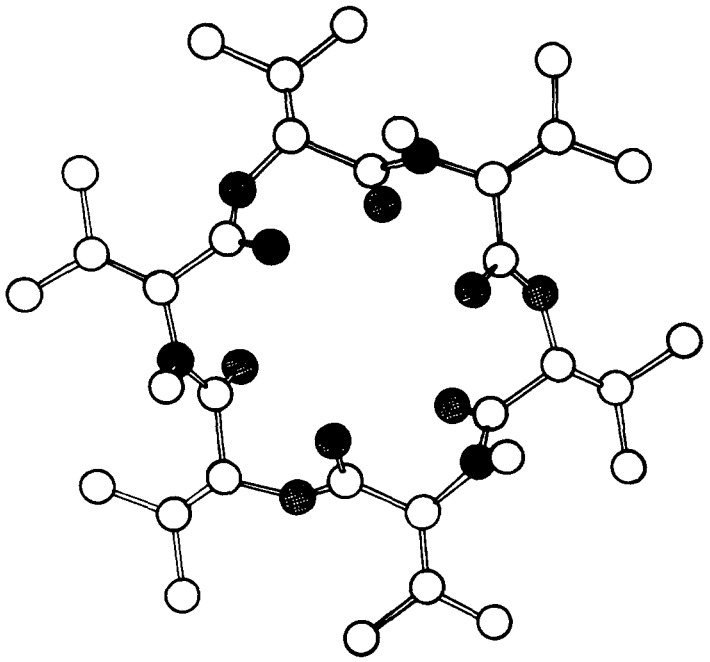


Fig. 4. Cyclic hexadepsipeptide with the three-fold axis of symmetry.

one above the other, but with a different direction of polarity gives symmetry $N2$. In such a way, the symmetry groups of peptides are: 1, N, $N2$. If radicals R are different, the symmetry (may be slightly distorted) is held only for the chain backbone—NH—CH—CO—while the arrangement of radicals is pseudosymmetric.

Secondary structure, polypeptides, fibrous proteins

When a large number of amino acid residues are joined together, some stable conformations of polypeptide chains arise which are called the secondary structure. One is the famous α-helix of Pauling and Corey (Fig. 5), the other is the β-structure of pleated sheets[9]. The α-helix is shown in Fig. 5. Its symmetry group is $G_1^3 = S_M$, $M = 18/5$, (i.e. 18 residues per 5 turns), the pitch of the helix 5,4 Å, projection of a residue on the axis $c' = 1{,}5$ Å, period of translation is $5{,}4 \times 5 = 1{,}5 \times 18 = 27$ Å. The α-helix is stabilized by hydrogen bonds NH—O between 1–4 residues along the chain. If all the residues are identical, the symmetry $S_{18/5}$ is a true one (this is the case of synthetic polypeptides). If the radicals are different, as in real proteins, this symmetry is observed only for the backbone, while different R_i are not equal to one another symmetrically, but their locations remain symmetrically related.

The α-helix shown in Fig. 5, is right-handed, it is thus called because it follows the right screw (amino acid residues are left-handed). One can build up the left-hand (i.e. left-screwed) helix, but it is less favourable energetically due to the packing in it of left residues, and is not observed in nature.

Many fibrous proteins—keratin, myosin and others—are built on the basis of the α-helix. But when the α-helices are packed into fibres, they are found to be slightly distorted, and helical superstructures of higher order are formed (Fig. 6)[10]. The triple chain collagen molecule represents one more type of helical protein structure[11].

The β-structure of polypeptide chains is shown in Fig. 7(a, b). The chains are arranged parallel to each other and are linked by hydrogen bonds. These structures are described by groups of layers $G_2^{3.1}$. The symmetry of an extended polypeptide chain with identical radicals is $S_2 = 2_1$; in crystallographic notation 2_1 is a two-fold screw axis, symmetry of the parallel β-pleated sheet is $2_1 t_1 t_2$ where $t_1 t_2$ are two translations in a sheet (Fig. 7(a)). The symmetry of an antiparallel β-pleated sheet (Fig. 7(b)) is $2_1 t_1 2_1 t_2 2$, screw axes 2_1 also arise along the second translation, whereas the rotation axes 2 are arranged perpendicularly to the sheet "piercing" it through. For example, silk fibroin is built according to the β-structure type.

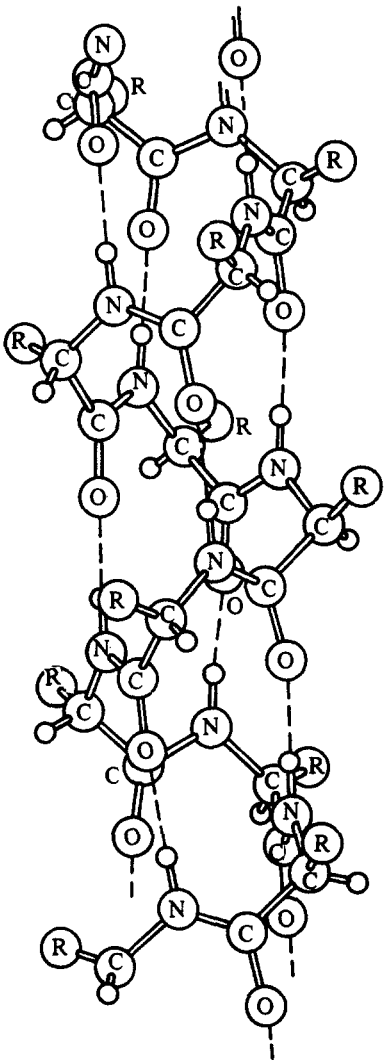


Fig. 5. The Pauling–Corey α-helix. R is a side radical of an amino acid residue.

Globular proteins, their secondary structure, supersecondary and tertiary structure

The molecules of globular proteins are the most complex atomic constructions of animate nature. A globular protein represents a single polypeptide chain (Fig. 8)[12] folded in a specific way into a globule, or an aggregation of several globules. The number of residues in a chain of various proteins ranges from dozens to several hundreds, the number of atoms in them, from hundreds to tens of thousands. Since a polypeptide chain consists of asymmetric amino acid residues and is folded in a certain way, a protein globule is always asymmetric, its symmetry being 1. However, such a globule is rich in pseudosymmetry and local symmetry. The structure of a globule is defined by the chemical sequence of radicals in a chain (8); this sequence is called the *primary* structure. After synthesis of the chain in a ribosome according to the genetic code, the chain, under cell conditions, folds spontaneously into a unique conformation which is inherent only in the given protein. All millions of molecules of the given protein are identical. It should be noted that some proteins contain molecules of non-protein nature—cofactors.

For the structure of a protein globule characteristic are:

(1) a strict periodicity repetition of the sequence of the backbone atoms $NC_{\alpha}C$, and the same periodicity of the attachment of side radicals. But this cannot be called the exact translational symmetry, because the chain is not straight, winding in a different way in space; it may be treated as topological translational symmetry;

(2) the stable symmetric α- or β-secondary structure arises locally on separate segments.

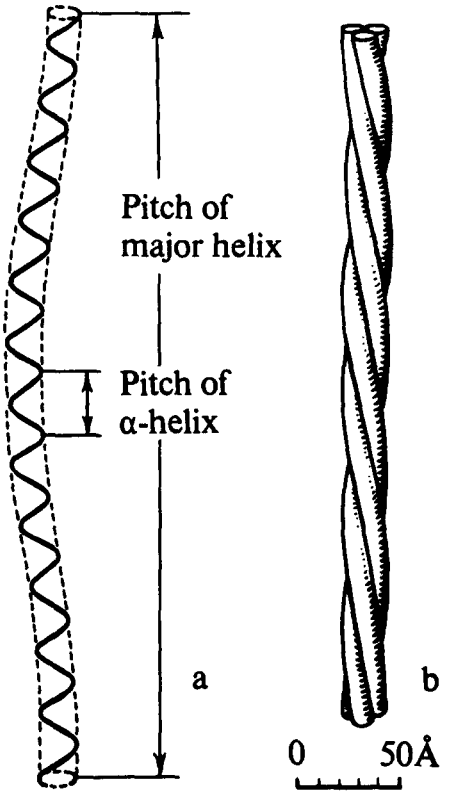


Fig. 6. Scheme of the structure of α-keratin: (a) the supercoiled α-helix; (b) three-stranded subfibril.

Between the segments of the secondary structure the chain has an irregular conformation;

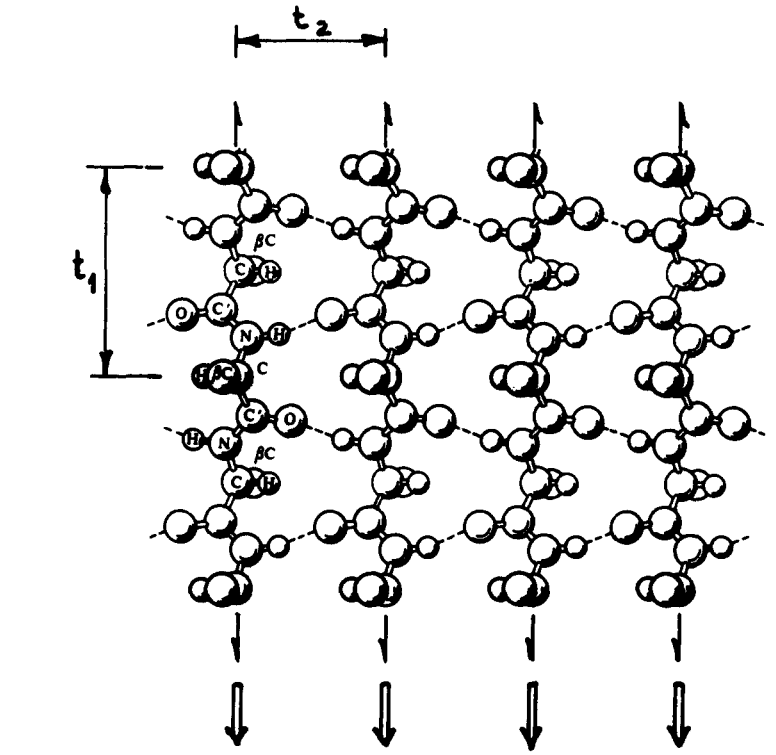
(3) the segments of the β or α secondary structure often aggregate into the secondary superstructure (Fig. 9);

(4) sometimes, separate parts of a folded chain, domains, can be observed in a globule.

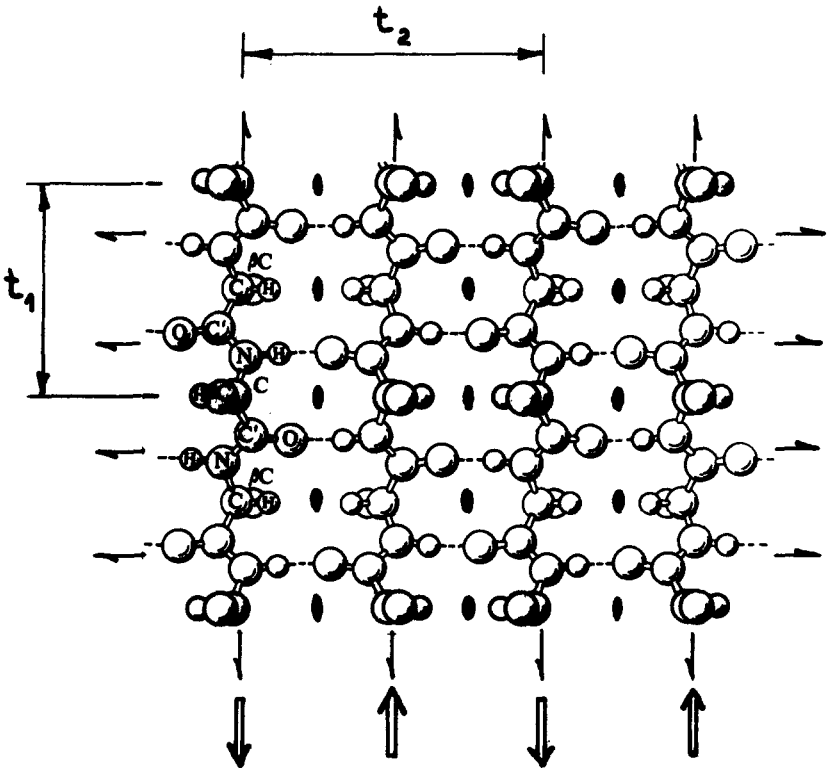
The spatial organization of a protein globule, as a whole, is called tertiary structure. The convenient way of describing the structure of protein molecules is the representation of β-chains by arrows, α-helices by helical ribbon or a cylinder, irregular chain by a lace (Fig. 9(a-c))[13,14]. Figs. 10–12 demonstrate some representatives of protein globules—hemoglobin[15], hemerythrin[16] (α-proteins), γ-crystallin[17] (β-protein), carboxypeptidase[18], catalase[19] (α/β proteins). An interesting variant of the secondary β-structure—the pleated β-sheet twisted into a propeller—is observed in carboxypeptidase (Fig. 12) and some other proteins. Catalase (Fig. 13) is a protein with the clearly expressed domain structure. Figure 14[14] shows some other variants of the superstructure of domains possessing (if the details of the arrangement of radicals are neglected and only the idealized course of the chain is considered) the fine symmetry whose analogs can be found on the ornaments of paintings of the ancients.

So, we can see, that in the structure of globular proteins there is a certain hierarchy. The primary elements of the structure are small protomolecules of amino acids. On the basis of chemical sequence of amino acids the spatial superstructure and the secondary structure are formed. As the result, the domains and, finally, tertiary structure of the entire globule come into being. The packing of atoms along the chains in the entite globule is rather dense (Fig. 14).

It should also be noted that the protein molecule is in a thermal motion, its vibrations are made up in such a way as to enhance the fulfillment of the biological function. When the molecule is functioning, its parts, especially at the active center, experience slight (0.5–1 Å), or more considerable (up to 5–10 Å) conformational shifts. The expedient, unique structure of protein molecules has been elaborated in the course of many hundreds of billions years of biological evolution on the Earth.



(a)



(b)

Fig. 7. Parallel (a) and antiparallel (b) β-structures. ↑, ⬮—two-fold axes, ↑—screw two-fold axe ↑↑—direction of chain.

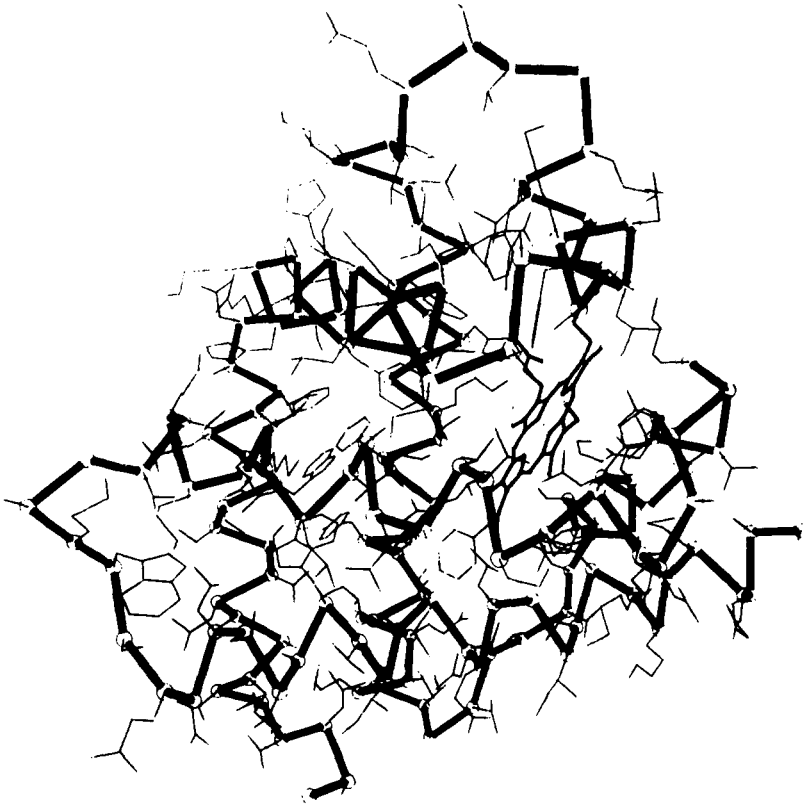


Fig. 8. Skeletal structure of the leghemoglobin molecule.

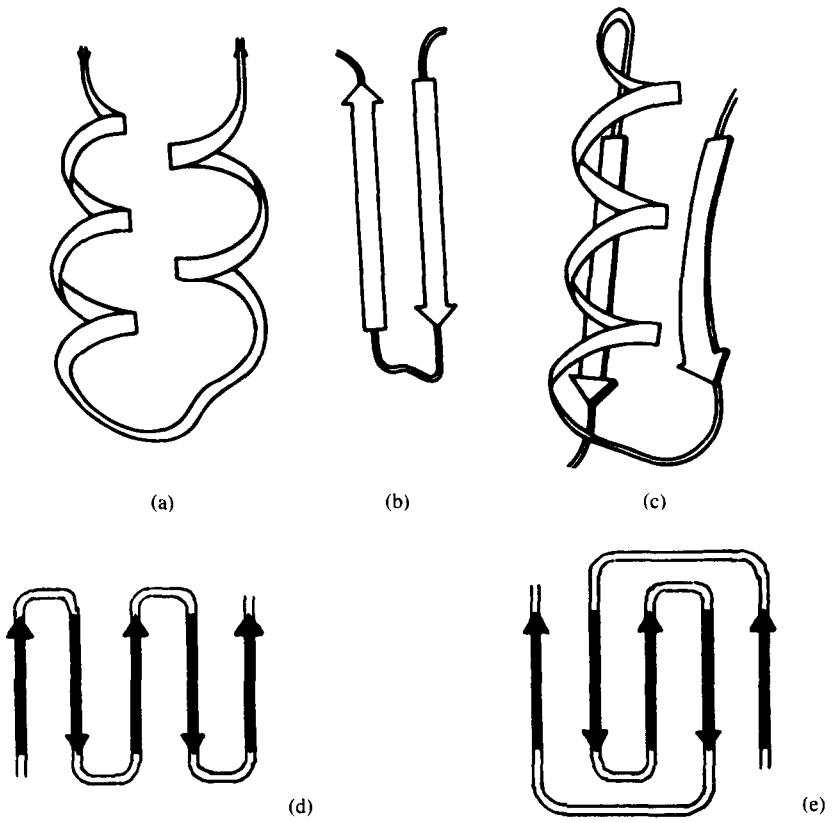
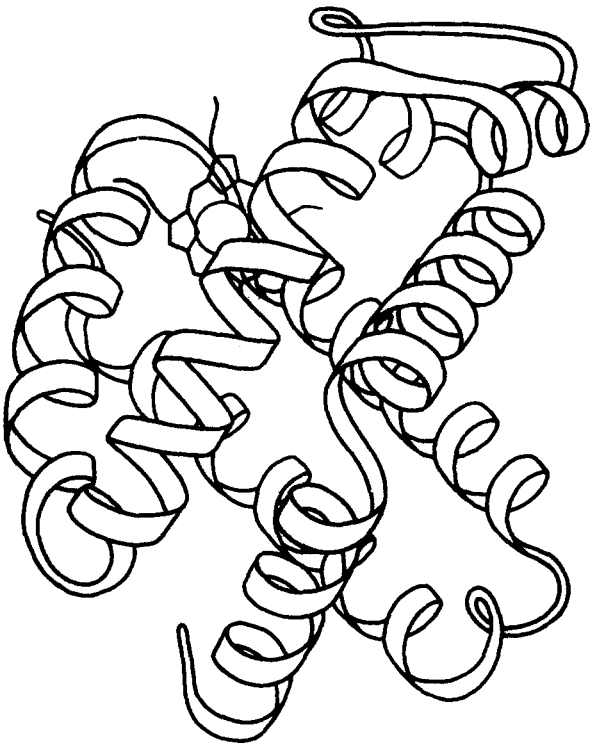
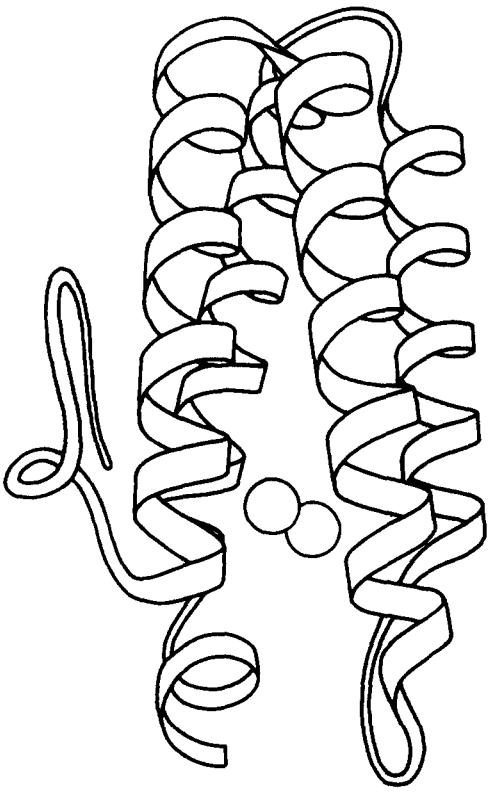


Fig. 9. Some elements of the supersecondary structure: αα (a); ββ (b); βαβ (c); typical variants of the β-structures: méandre (d); Greek key (e).



(a)



(b)

Fig. 10. Polypeptide chain folding in the structures of α-proteins: hemoglobin β-subunit (a) and hemerythrin (b).

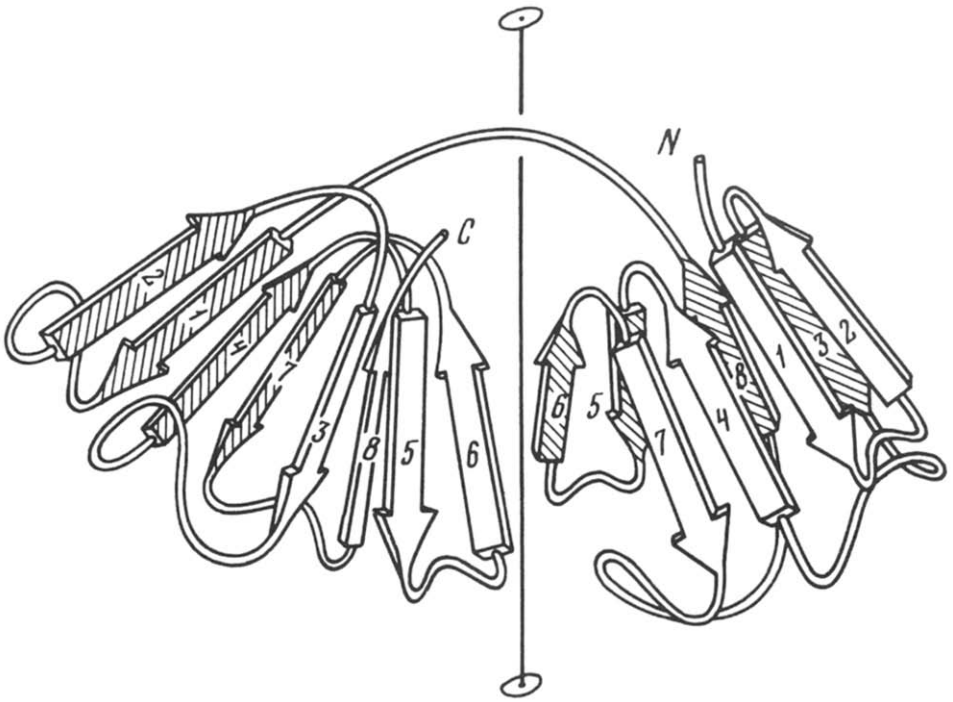


Fig. 11. γ-crystallin. An example of β-protein.

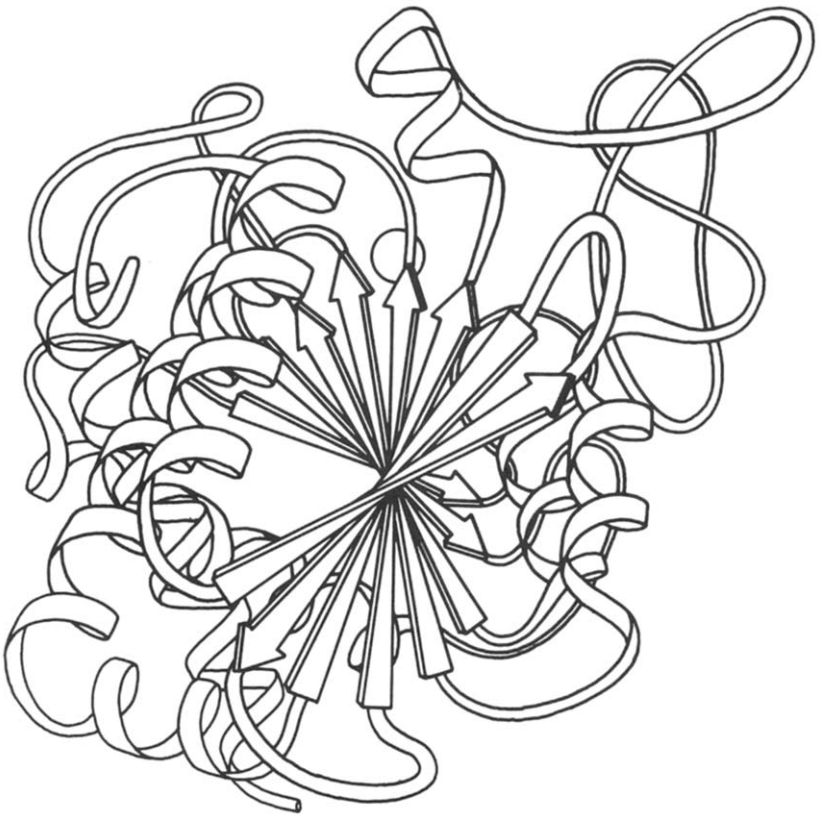


Fig. 12. Carboxypeptidase. An example of α/β-proteins.

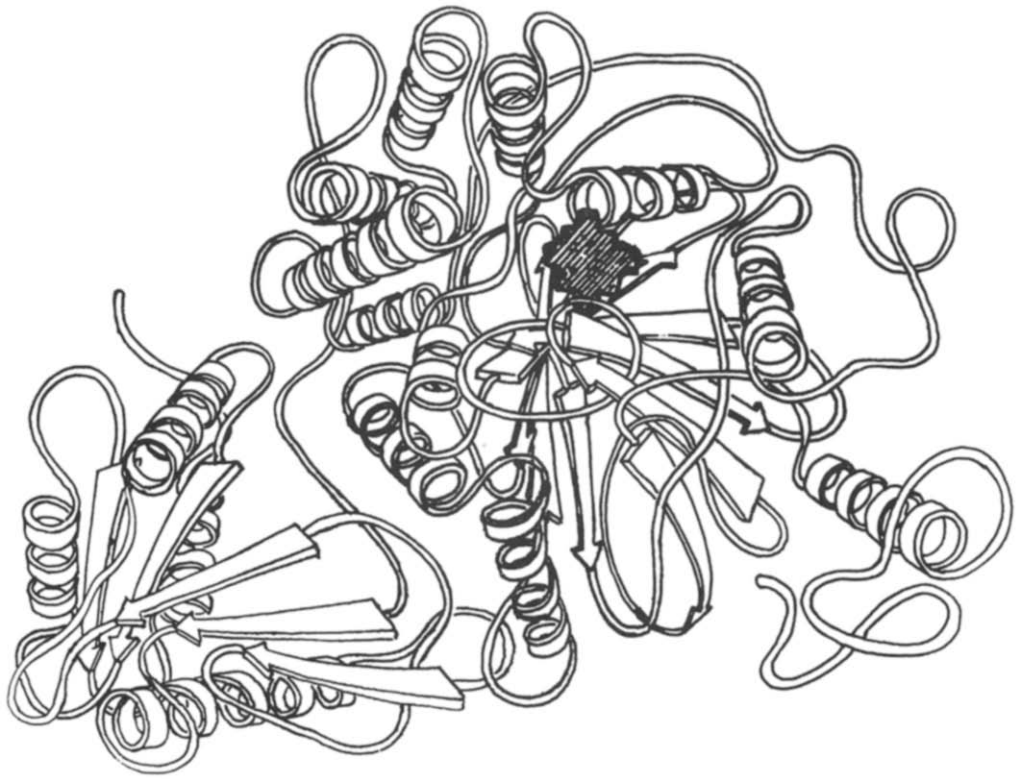


Fig. 13. A subunit of α/β-protein catalase Penicillium Vitale consisting of three domains.

The quarternary structure

The quaternary structure is the aggregation of several globules into one symmetric association. This level of organization, next to the tertiary structure, is observed in many proteins. In this case, the globules being joined together are called subunits, the form of their contacting surface is complementary. The proteins with the quaternary structure are depicted by the point groups $G_0^{3,I}$.

The quaternary structure of proteins is revealed by X-ray structure analysis; the effective method of its investigation is electron microscopy in combination with the mathematical method of three-dimensional reconstruction[3].

The formation of associations of protein globules is due to the attractive forces between them. These interactions may be electrostatic or van der Waals and hydrophobic ones. Figure 15(a, b) shows a scheme for interaction leading to the appearance of symmetry. It is facilitated by complementarity: the intersupplement of the form of contacting parts. Complementarity is one of the clearly expressed principles of organization of biomolecular structures. The association of globules enables the improvement of protein functioning. This can easily be explained when the active center of a molecule is formed on the adjacent parts of subunits, i.e. when the amino acid residues of different segments of the chain in the subunit take part in the fulfillment of the active center function. One example is aspartate aminotransferase (Fig. 16)[20]. In other cases, the active center is located far away from the boundaries of contact, as in catalase (Fig. 17), but the aggregation of subunits still exerts influence on the function, probably on account of electron structure, electrostatical potential of subunits, change in their thermal motion. This is clearly demonstrated by the fact that, on dissociation into subunits, the activity sharply decreases.

The most frequently encountered point symmetry groups of the quaternary structure of proteins are: 2,222 (tetrahedral), 32, 42.

Very interesting is the case when protein functioning prompts a change in the quaternary structure. The classical example is hemoglobin consisting of four pairwise identical subunits[21]. The exact symmetry of the molecules is 2, but, since the subunits are very similar in structure, the pseudosymmetry is tetrahedral 222 (Fig. 18). In hemoglobin, owing to the cooperative steric interaction, the function of binding and transfer of O_2 is much improved as compared with monomeric (consisting of one subunit) proteins of this type. An oxygen attachment involves

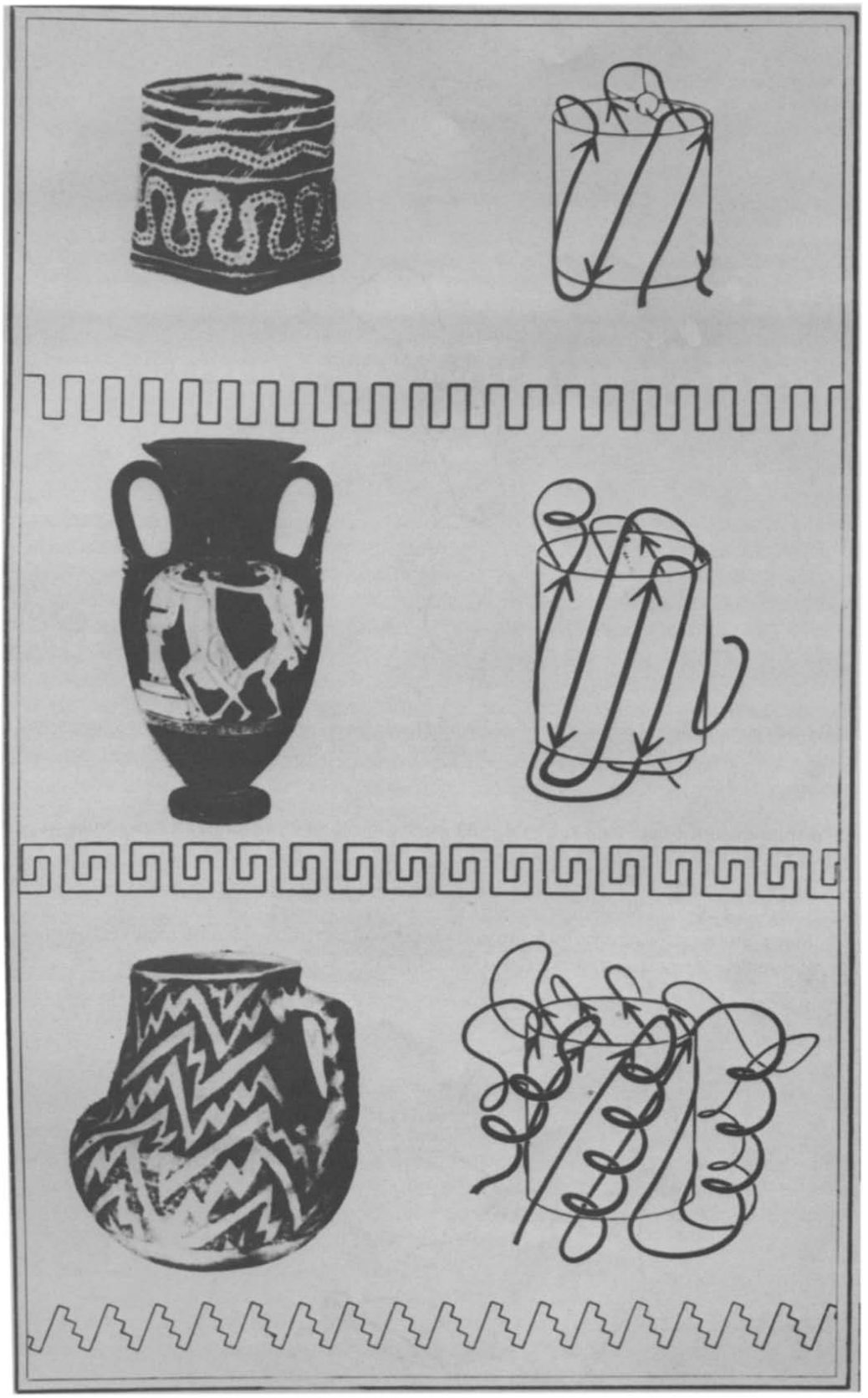
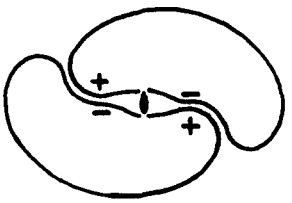
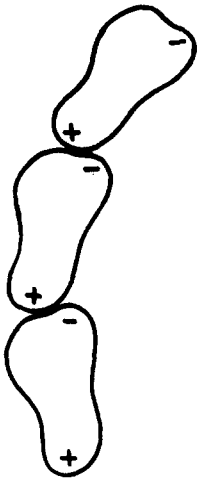


Fig. 14. Geometrical motifs in cylindrical β-sheets and comparison with the ornaments on paintings of the ancients. Top: β-sheet in rubredoxin, middle: in preabumin, bottom: β-sheet covered by α-helices in triose-phosphate isomerase.



(a)



(b)

Fig. 15. Electrostatic and other forces of interaction of the surfaces of molecules may promote their joining into finite (a) or infinite (b) associations (+, − charged parts of a surface).

the displacement of subunits, the molecule stands out as if "breathing," preserving its symmetry 2.

Sometimes, the subunits of a molecule serve for different tasks, e.g. some subunits are regulatory and the others are functional (Fig. 19)[22].

Some proteins form very intricate complexes composed of subunits of several sorts with the total molecular mass up to millions (Fig. 20)[23].

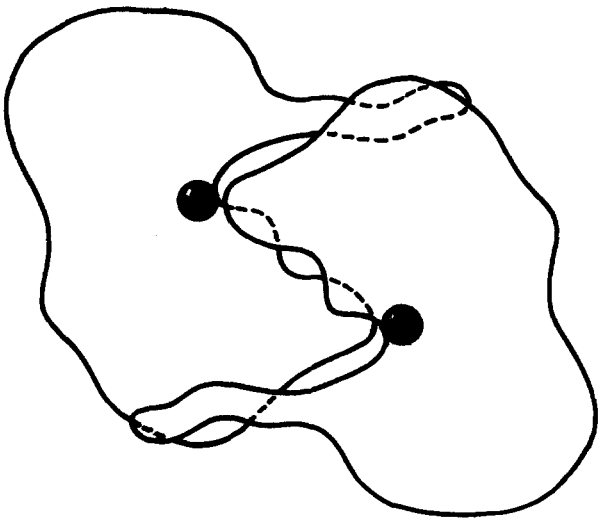


Fig. 16. Aspartate aminotransferase dimer, circles active center (model at 5 Å resolution).

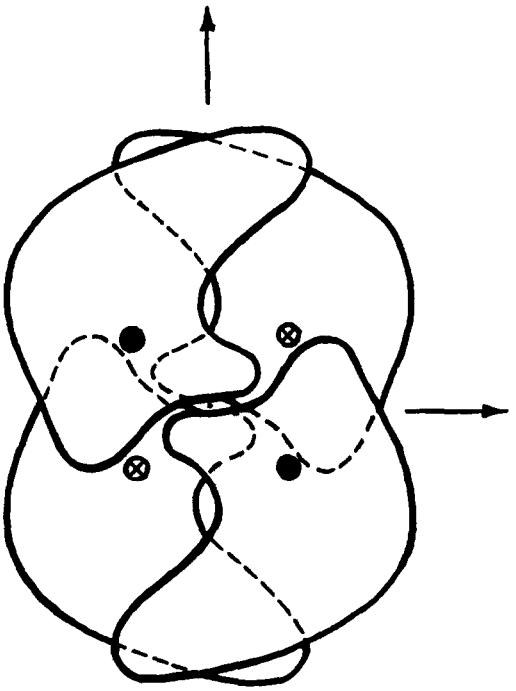


Fig. 17. Scheme of a catalase tetramer, circles active centers (cf. the monomer structure, Fig. 13).

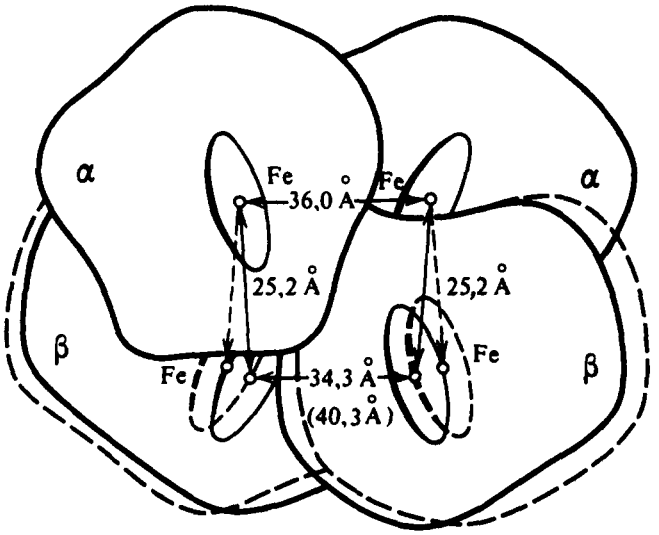


Fig. 18. A change in the quaternary structure of a hemoglobin tetramer in the course of oxygenation (solid line—deoxygenated form).

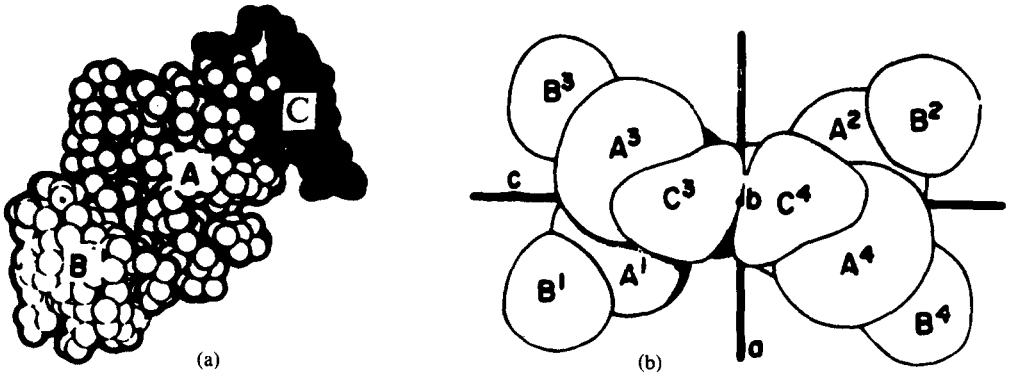
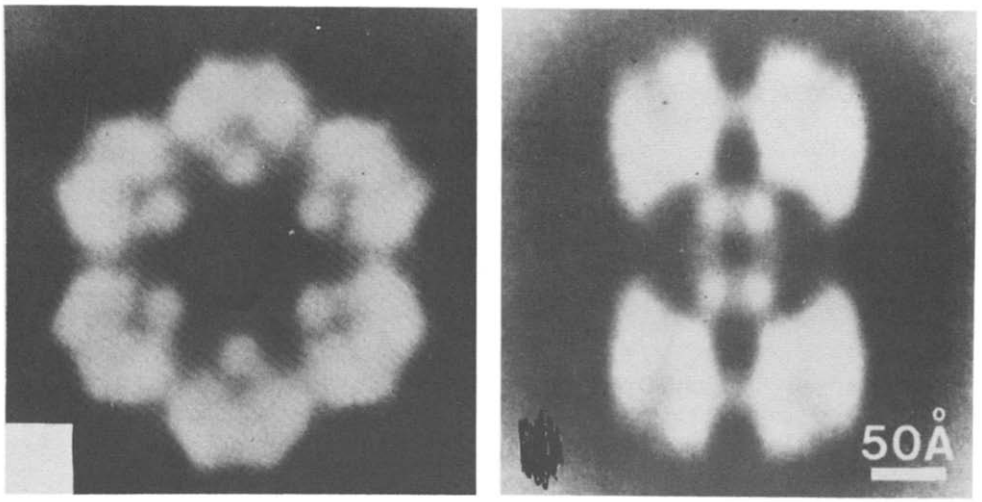


Fig. 19. The domain (a) and the quaternary (b) structure of piruvate-kinase.



(a) (b)

Fig. 20. Complicated quaternary structure of Lumbricus annelid hemoglobin complex. Symmetry of the molecules—62, pseudosymmetry 6mm; (a) view along axis 6, (b) view along axis 2.

Some evidences indicate that the joining of the substrate molecules to the subunits does not occur simultaneously. In these cases the ideal symmetry of a quaternary structure is disturbed, but, pseudosymmetry is, certainly, retained. It should also be remembered that the "ideal" symmetry is really the averaged symmetry on account of the thermal motion of the atoms and their groups around their equilibrium positions in a protein molecule.

Spherical viruses

The "task" of a virus particle is to introduce the nucleic acid into the host cell, which, making use of a protein-synthesizing machinery of the cell, makes it to produce not its own proteins, but proteins of the virus particle.

The simplest viruses—"spherical" or, to be more precise, icosahedral—consist of a protein capsid (the container), and RNA stored in it. The protein shell should be constructed most

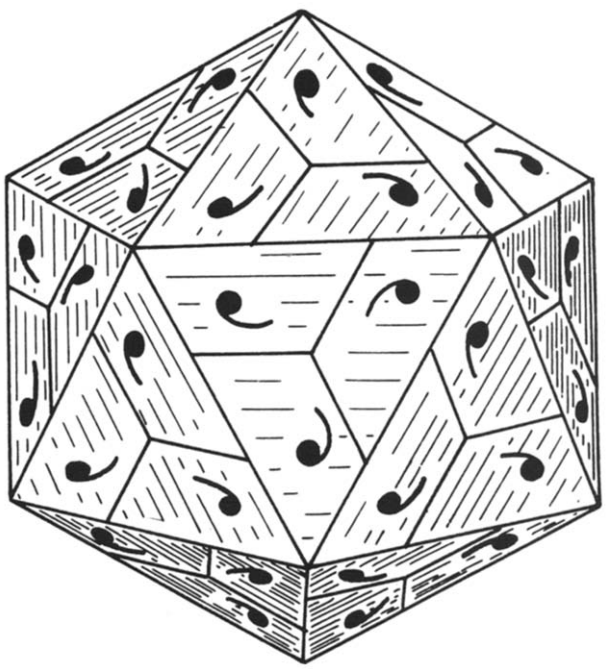
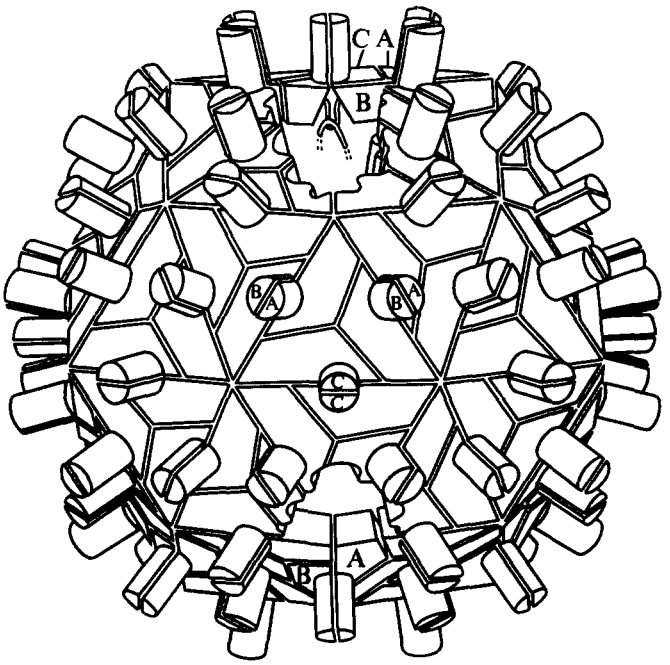


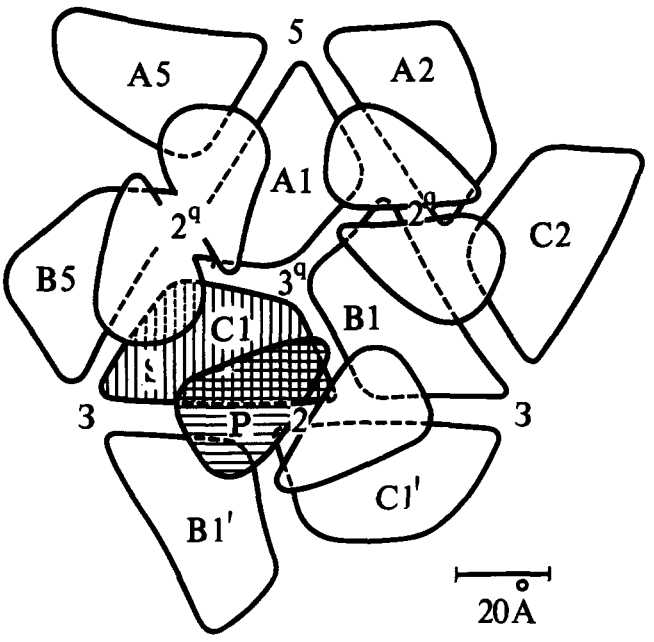
Fig. 21. Icosahedron. Asymmetric units are shown denoted by commas.

economically, i.e. should embrace the largest volume at the smallest surface. This is achieved when its shape approximates most closely the spherical one[24]; this requirement is best satisfied by shells with icosahedral point symmetry 532 (Fig. 21).

The order of this group is $n = 60$, therefore the number of asymmetric protein subunits S is a multiple of 60. The subunits join into pentamers $P = 5S$ which lie on the exit points of axes 5, the number of pentamers being 12. In simplest case, the virus is made only of 12 pentamers. In other cases, the virus also possesses hexamers $H = 6S$, the number of hexamers is $10(T - 1)$, T is the so-called triangulation number which may be equal to 1, 3, 4, 7 . . .[24]. In the tomato bushy stant virus there are 180 subunits. The hexamers lies on the exit points of axes 3 and between them there arise additional axes of quasisymmetry 3^q and 2^q (Fig. 22)[25].



(a)



(b)

Fig. 22. Tomato bushy stunt virus: (a) general scheme of subunit packing, (b) the arrangement of subunits between axes 5, 3, 2; quasiaxes 2^q and 3^q are shown.

Recently, it has been found that some icosahedral viruses may be made completely of pentamers P which are arranged not only on axes 5, e.g. the polyoma virus consists of 360 pentamers[26]. The RNA chain inside the virus is asymmetric, but, apparently, its loops fit, to some extent, the regular packing of subunits in a capsid.

The shape of protein subunits in icosahedral viruses is specially designed for their complementary packing just into an icosahedral shell. (The attempts to crystallize the virus subunits into true three-dimensional crystals have so far failed.)

Helical packing of protein molecules

Globular proteins often aggregate into associations with helical symmetry S_M. On the basis of the relation of the particle size to the radius of the structure R they can be subdivided into thread-like $d/R \sim 1$, rod-shaped $d/R \sim 1{,}2$–$1{,}5$ and tubular $d/R \sim 2$–3 ones (Fig. 23).

The examples of thread-like structures are protofibrillae of actin—the protein of muscle forming a two-pitch helix with symmetry S_{13} (Fig. 24)[28].

The classical example of rod-shaped structure is tobacco mosaic virus TMV[29]. The 2140 elongated protein subunits of TMV are packed into a rod with $M = 49/3$. The RNA chain is found to be helically folded closer to the rod axis (Fig. 25). The conditions may be provided in which the subunits are packed into discs with the 17th-fold axis of symmetry ($49/3 \approx 17$), such discs are considered as an intermediate stage of rod formation[30].

The function of viral protein subunits is not only the storage of nucleic acids, but also the interaction with the host cell in order to adhere to it and penetrate into the cell. This function finds its vivid expression in the structure of bacteriophages representing a complex mobile molecular apparatus constructed on the clearly expressed principles of symmetry.

Let us consider, as an example, the structure of bacteriophage Phy 1 E. coly (Fig. 26)[31]. Its head contains DNA, possesses pseudoicosahedral symmetry and has (attached to it by the neck) a tail consisting of a rod with an inner channel and a sheath whose protein subunits are dimers. The symmetry of particle packing in the tail in its intact state is $S_{7/2}.6$, the sheath appears to consist of flat discs about 40 Å thick with six subunits in each. The discs are superimposed one on another with a 103° rotation and a period 252 Å (Fig. 26(b, c)). The phage is attached to the cell by means of the basal plate and tail fibers; this device also has the 6th-fold symmetry (Fig. 26(d)). When coming into contact with the cell, the basal plate rearranges, still preserving symmetry 6 (Fig. 26(c)) and initiates the sheath contraction: the disc subunits rotate and the discs enter one into another more closely, the sheath symmetry is $S_{11}6$. As for the rod, it preserves its structure and enters the cell; through its channel DNA stored in the head is "injected" into the cell.

In larger viruses the symmetry is not revealed so clearly as in the viruses described above, but pseudosymmetry in the structure of the shell and some other parts is preserved.

Tubular crystals of proteins

It has been found[32] that some globular proteins can be associated into tubular structures, the geometrical scheme of which is shown in Fig. 27. The symmetry of these structures is S_M, they can also be described as a two-dimensional layer rolled up into a cylinder. Owing to a high regularity such structures may be called "tubular crystals." Fig. 28(a) shows an image of a phosphorylase b tube[33], Fig. 28(b) represents three-dimensional reconstruction of catalase tubes, symmetry $G_1^{3,1} \approx S_{92/11}$[34]. The natural, *in vivo*, tubular structures are known for tubulin. The formation of a tube with monomolecular walls may be explained by a selective character of interaction between protein molecules, "sidelong" (along the wall surface) attraction of molecules and the respective complementary shape.

Layers

The number of proteins, including catalase and phosphorylase[33] form two-dimensional plane monomolecular layers with symmetry $G_2^{3,1}$; but such layers arise only on flat supports. The most important example of native layered structures are membranes consisting of a double layer of lipid molecules (Fig. 29). The twice-periodical symmetry is expressed in membranes, but only roughly, it approximates the statistical symmetry of smectic liquid crystals[36].

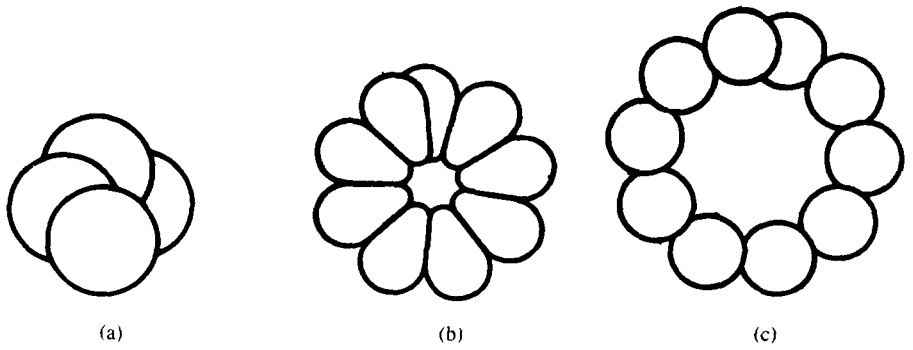


Fig. 23. Scheme of the subunit packing projection along the helical axis in thread-like (a), rod-shaped (b) and tubular (c) helical structures.

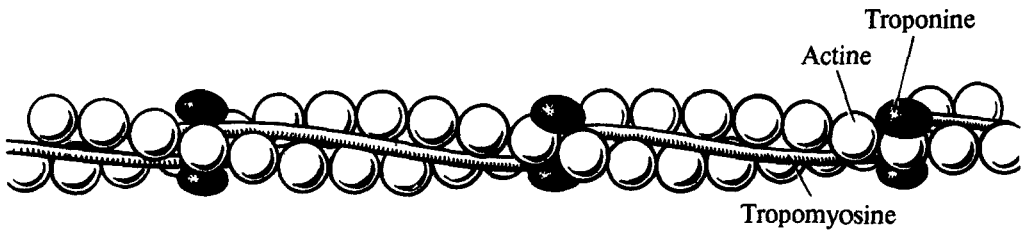


Fig. 24. Actin protofibrillae with proteins laid out on them—troponin and tropomyosin.

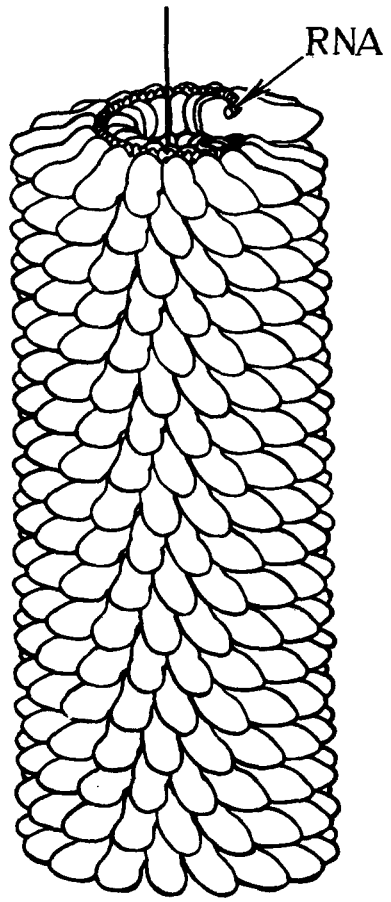
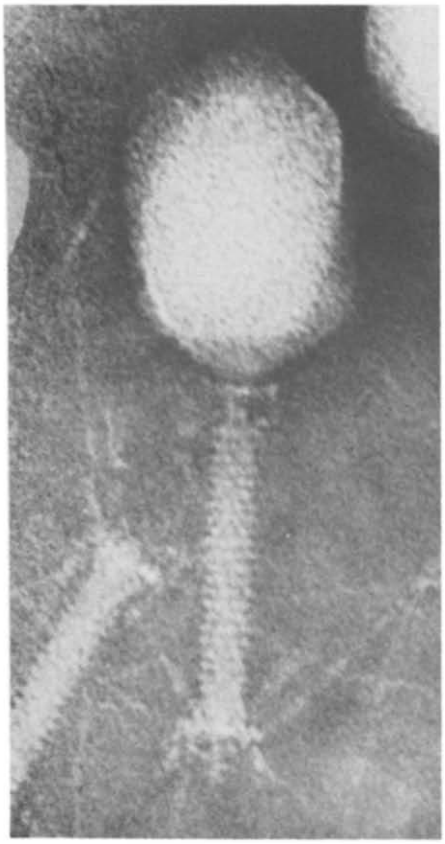
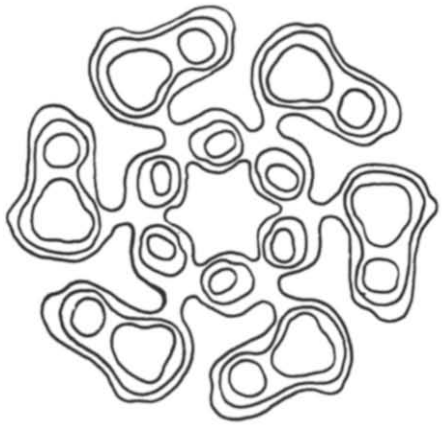


Fig. 25. Packing of protein subunits in tobacco mosaic virus.



(a)



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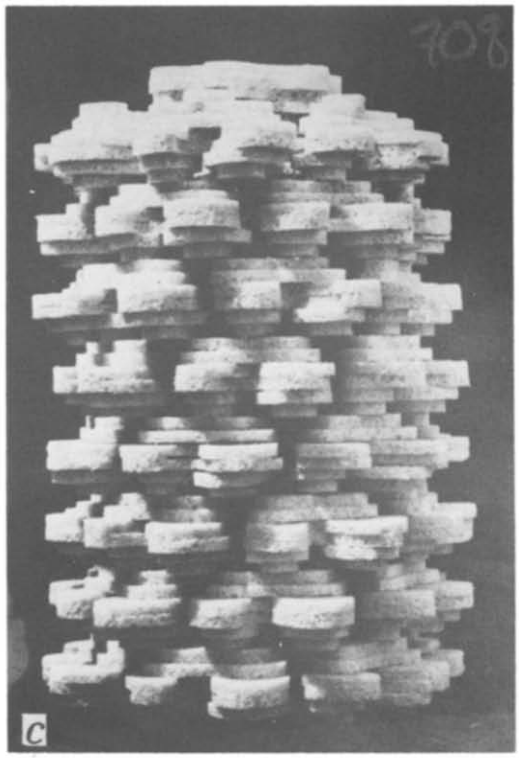
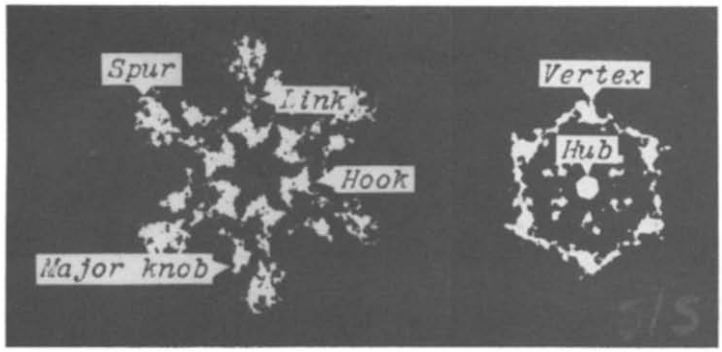


(c)



(d) (e)

Fig. 26. (a) Electron micrograph of phage Phi-1 in intact state; (b) scheme of one disc of the rod and sheath; (c) three-dimensional reconstruction of the rod and sheath; basal plate in intact (d) and contracted (e) states.

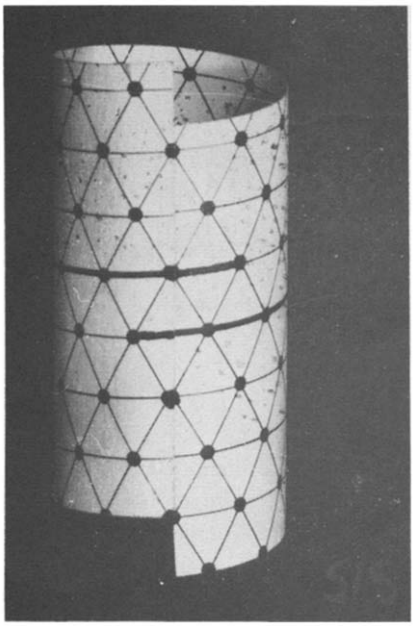
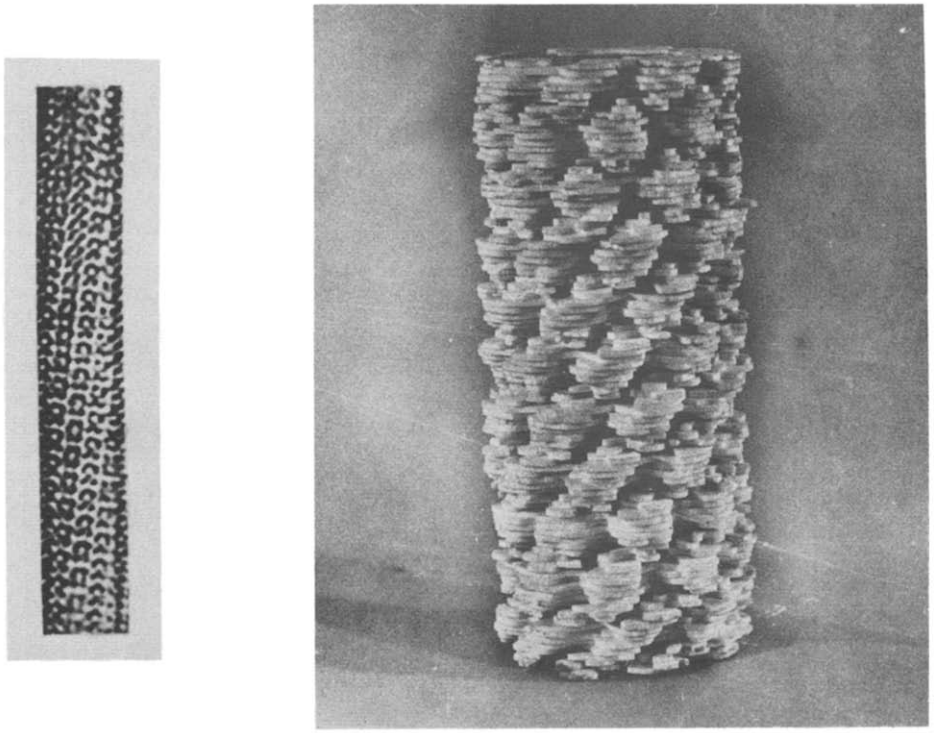


Fig. 27. Geometrical scheme of a tubular structure.



(a) (b)

Fig. 28. Tubular crystals of proteins: (a) phosphorylase b, an electron microscopic image, optically filtered; (b) ox-liver catalase, three-dimensional reconstruction.

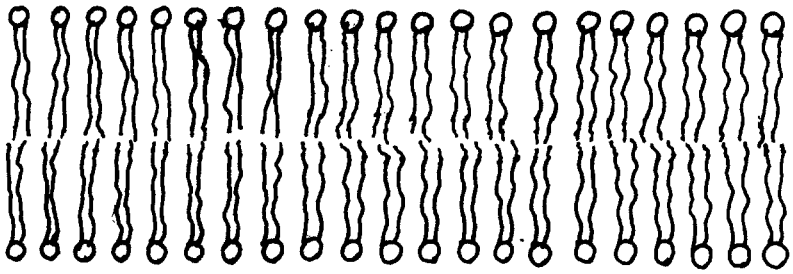


Fig. 29. Double layer of molecules in a membrane.

The structure of DNA

The secondary structure of DNA is the famous Watson–Crick double helix (Fig. 30). Its symmetry clearly emphasizes and reveals the main DNA function: the storage and possibility of reading out and duplicating genetic information. Two phosphate-sugar (4) chains are strictly periodic and are linked by complementary hydrogen-bonded pairs of the A—T and G—C bases. Symmetry of the structure is S_M2, axes 2 are perpendicular to the axis of the helix, so that both polar chains run in the opposite direction. The double DNA helix is right handed. For the bases, symmetry S_M2 is the pseudosymmetry, it only indicates the position and orientation of an "averaged" base in space. The distance between the planes of the base pairs is equal to 3, 4, Å. In the main B-form $M = 10$, i.e. the double helix makes the complete revolution with the period 34 Å. In the other A-form the base planes are not perpendicular to the main axis of the helix, $M = 11$.

Recently, it became possible to synthesize short oligonucleotides with the number of bases from 4 to 12[37,38]. Such oligonucleotides are of special interest when they are self-complementary, as, e.g., in a dodecamer

CGCGAATTCGCG

GCGCTTAAGCGC.

Such a molecule represents a palindrome—it is identical when read out in both directions. Oligonucleotides may be crystallized, they form a three-dimensional crystal structure which renders to an accurate X-ray diffraction analysis (Fig. 31). Symmetry S_{10} is preserved for the right-handed double chain, and in the case of self-complementarity there exists one true axis 2 which passes through the center of the oligonucleotide[37]. There has also been found an unusual, left-handed, with respect to helicity DNA form—the so-called Z-DNA[39].

In the cases where DNA or RNA is arranged into a tertiary structure inside viruses, chromosomes or ribosomes, they have, in some parts, the double-helical secondary structure described above, but at other parts they also exhibit an irregular conformation with an unbraided single chain. The asymmetric globular molecule of *t*-RNA is built up in the same way (Fig. 32)[40].

In the quaternary structure of elements of chromosomes—nucleosome—the special globular proteins, histones, are attached to the double RNA helix consisting of 140 pairs of nucleotides, DNA is bent over its main axis. This bent molecule forms a sloping superhelix with $1\frac{3}{4}$ turns and pseudosymmetry 2, axis 2 being perpendicular to the superhelix axis (Fig. 33)[41].

Biomolecular crystals

One can manage to crystallize many proteins, oligonucleotides, spherical viruses into true crystals with three-dimensional periodic packing $G_3^{3,1}$. The biocrystal formation can hardly assist the molecule in the fulfillment of some or another biological function. Therefore, such crystals in vivo are rarely observed—only as "stores" of the cell products which, when necessary, are utilized. For instance, it is known that the pancreas cells contain insulin crystals[42], some viruses are also crystallized in cells (Fig. 34).

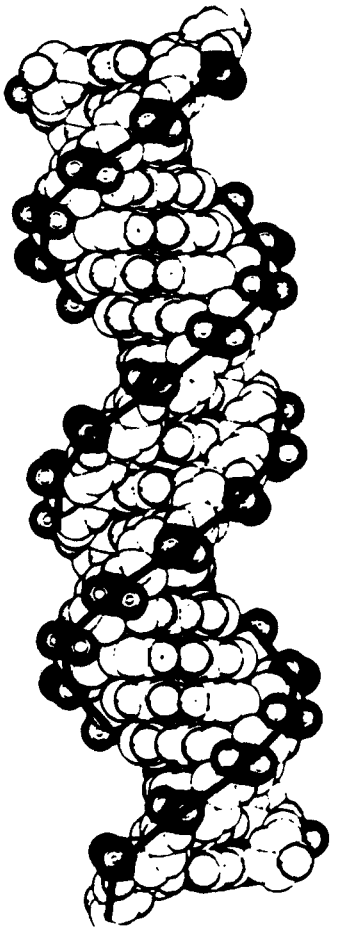


Fig. 30. DNA structure, B form.

At the same time, the purified preparations of biomolecules may be crystallized in vitro (Figs. 35, 36). The crystals contain, in the space between the molecules, the mother liquor and are stable only in the presence of this liquor, most frequently, this is water with some ions (Fig. 37). The water content in protein crystals constitutes from 30 to 70%, in crystals of *t*-RNA or oligonucleotides the solvent content reaches 90%. Thus the crystals of biomacromolecules are very peculiar systems which combine strict spatial periodicity and orientation of these molecules with liquid disordering of solvent molecules.

Such inwardly-two-component crystalline systems are not known to exist in inorganic and simple organic compounds. As some kind of analogy, we may take metals in which ionic skeltons of atoms are in the "gas" of free electrons surrounding them. The symmetry groups of crystals are Fedorov space groups $G_3^3 \equiv \Phi$, 230 in number. Of them, only 65 groups of the first kind $G_3^{3,1}$, containing only the simple or screw axes of symmetry (groups *C* and *D*, according to Schönflies nomenclature) are possible for biocrystals. Statistics of X-ray structural works on proteins (at present, such investigations run to hundreds) shows that there are only several Φ^1-groups which are favourable for proteins. These groups are the following: $P2_12_12_1$, (D_2^4)—23%, $C2$, (C_2^3)—13%, $P2_1$, (C_2^2)—11%, $P3_121$, (D_3^5) and $P3_221$, (D_3^6)—10%, $P2_12_12$, (D_2^3)—5%, $P4_122$, (D_4^4) and $P4_322$, (D_4^8)—4%, PI, (C_1^1)—4%. These groups depict 70% of protein crystals. Obligatory for all the groups (except asymmetric group $P1$ containing only translations) is the presence of screw axes, mainly, 2_1, which may be combined with other screw or rotational axes. The groups containing only the rotational axes, e.g. $P222$, are not, in general, observed.

A definite preferable population of some space groups is also known for inorganic and simple organic compounds. For them, such a population can be explained, mainly, by the principle of maximum filling (close packing) of the crystal volume by atoms and molecules[36,43]. In the case of proteins, these considerations are not decisive due to the above

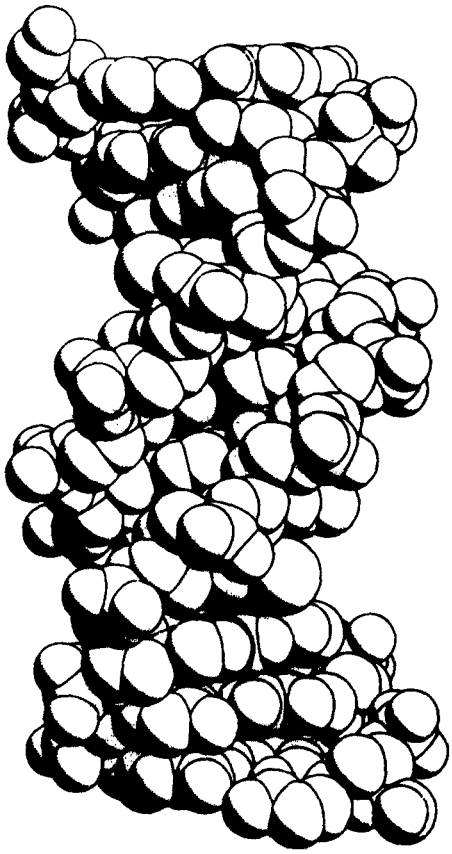


Fig. 31. Oligonucleotide duplex of 12 pairs of bases.

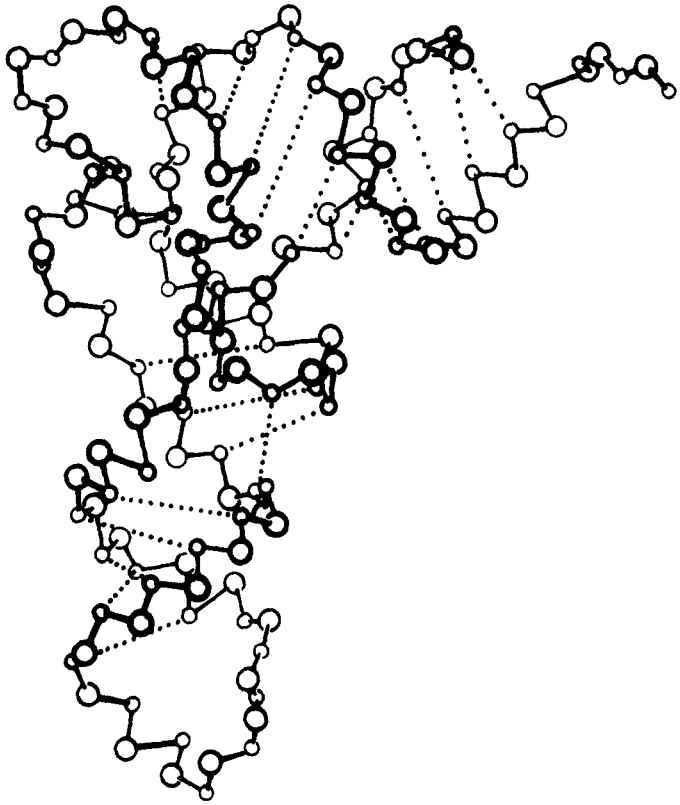


Fig. 32. *t*RNA molecule.

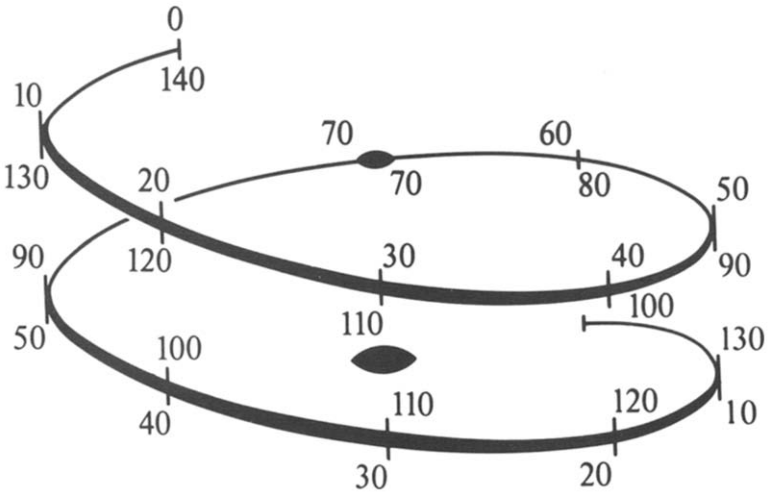


Fig. 33. Scheme of the arrangement of two-helical DNA strand in nucleosome.

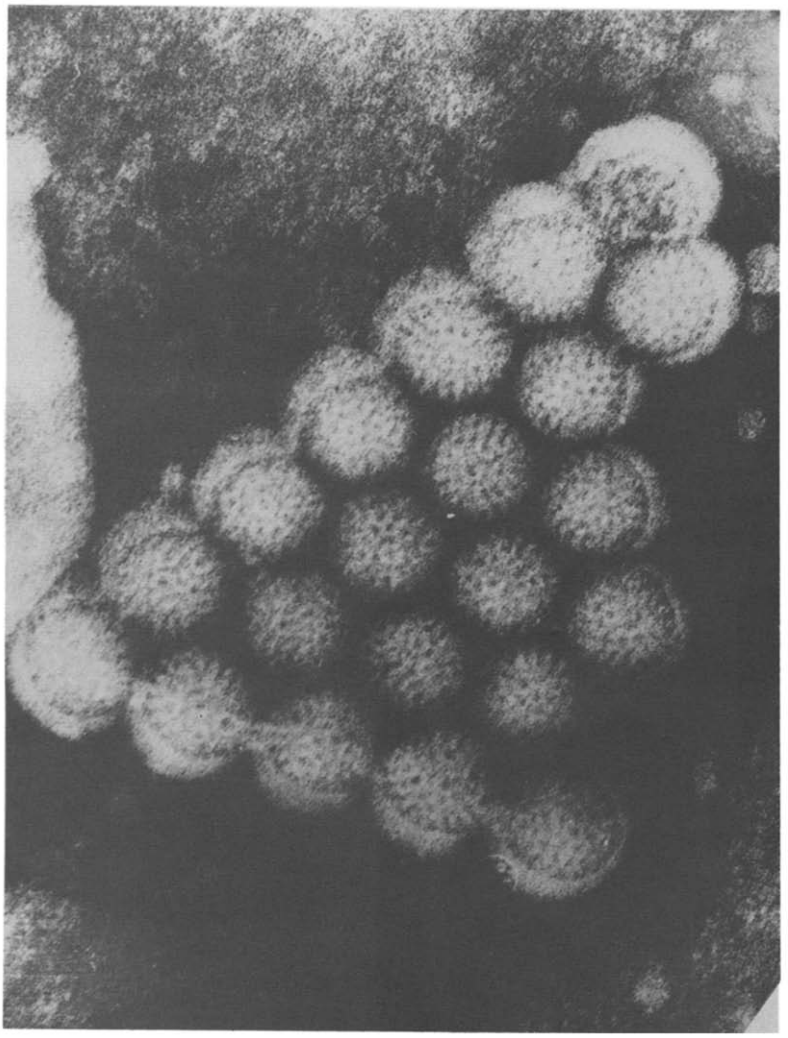
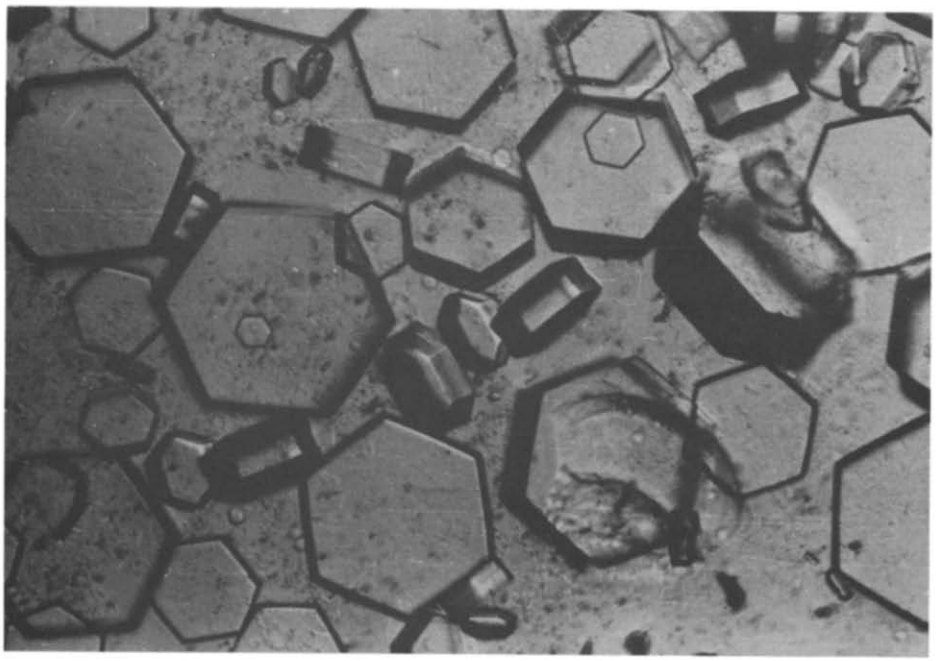
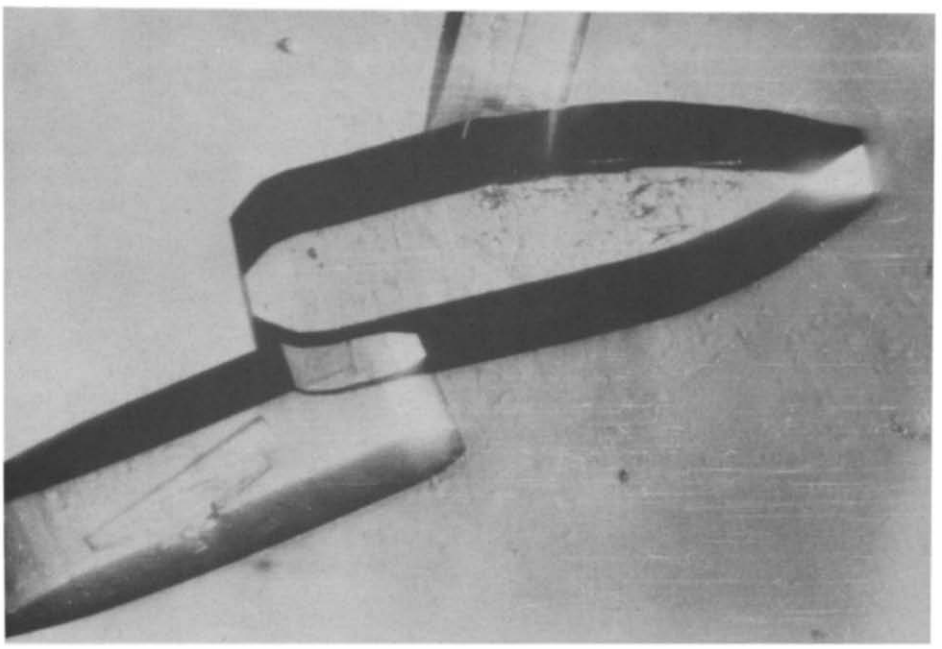


Fig. 34. Crystalline packing of particles of human rota virus. Electron micrograph, × 200000. (Courtesy of M. B. Korolev.)



(a)



(b)

Fig. 35. Protein crystals: (a) histidinedecarboxylase, (b) pyrophosphatase (× 30).

mentioned peculiarity in their structure—the possibility of filling up the space between the molecules by solveint. The forces which are acting when the molecules pack themselves into a crystal are, for the most part, electrostatic, and, in this case, the arising of screw arrangements is most probable (Fig. 15b).

In the arrangement of protein molecules with the quaternary structure into a crystal, one can often observe the discrepancy between the proper symmetry of the molecule and the

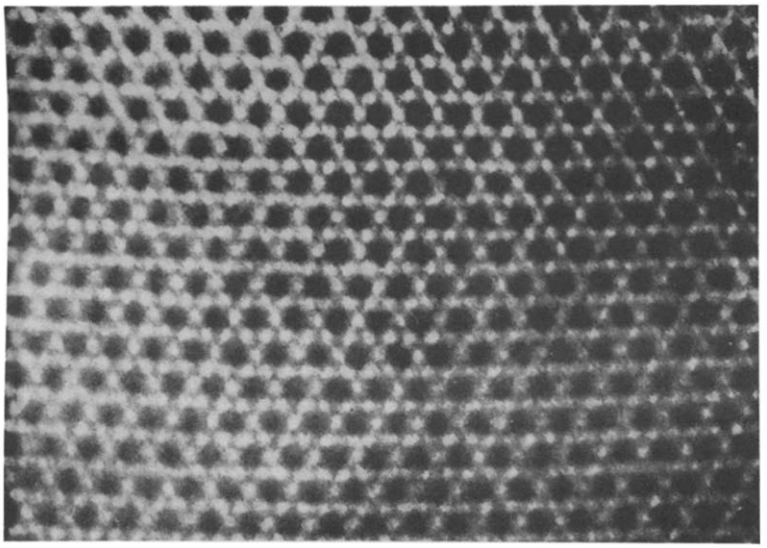


Fig. 36. Packing of the molecules in ox-liver catalase crystal. Electron micrograph, × 400000.

symmetry of its position defined by a space group. For instance, the point symmetry of catalase is 222 (Fig. 17), space group $P3_121$; when packing into a crystal, only one of the three axes 2 of the molecule coincides with axis 2 of the crystal, while the other two only depict the molecule. It turns out that in the asymmetric unit of the crystal A_{cr} there are arranged two symmetrically-equal (on the point symmetry of the molecule) parts A_M of the molecule, the stereon of the crystal is twice as large, by volume, as the stereon of the molecule: $V_{A_{cr}} = 2V_{A_M}$. A crystalline modification of catalase is known in which the entire molecule is placed in A_{cr}, i.e. none of the elements of point symmetry 222 of the molecule coincides with the elements of symmetry of the crystal, here $V_{A_{cr}} = 4V_{A_M}$[19]. Such cases are called noncrystallographic symmetry of the molecule in a crystal. Another example is aspartate aminotransferase (Fig. 16)[20] with space group $P2_12_12_1$, a symmetric dimer $2A_m$ with axis 2 is arranged in A_{cr}. Sometimes A_{cr} contains two (or more) asymmetric molecules of protein having no quaternary structure. And here $V_{A_{cr}} = 2V_{A_M}$, too, but the molecules do not transform one into another by some or other operation of point symmetry.

On the other hand, the symmetry of position in a crystal may coincide exactly with the point symmetry of the molecules. The cause of the arising of noncrystallographic symmetry or

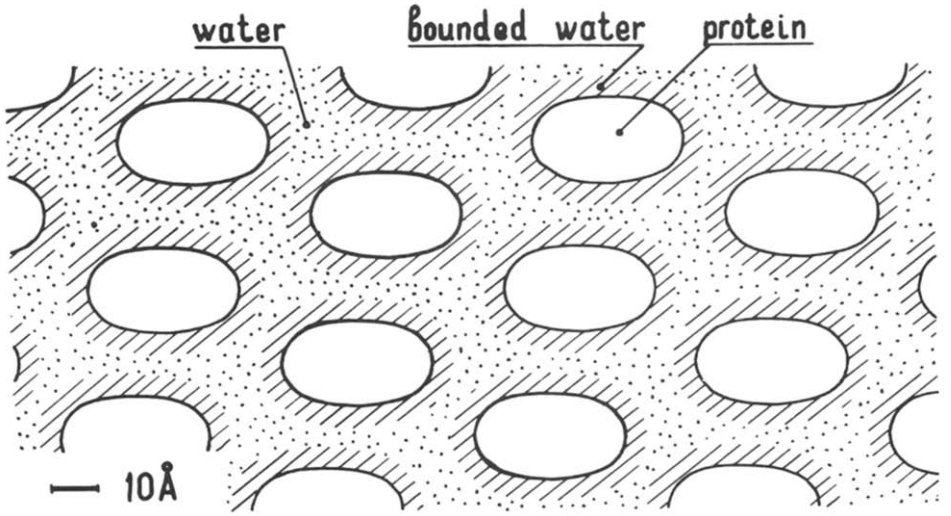


Fig. 37. Scheme of the structure of a globular protein crystal. The layer of ordered water molecules is linked with a protein molecule (hatched), the solvent molecules are shown by dots.

the presence of a pair of molecules in the asymmetric unit lies in the fact that dominating for a crystal is the attainment of the molecular packing giving the energy minimum. And this can be achieved both with use of proper point symmetry of molecules, when it partly or completely coincides with the symmetry of the crystal, and without such a coincidence. Noncrystallographic symmetry is one of the expressions of the symmetrization-dissymmetrization principles of Curie and Neumann for component physical systems[1,44].

Conclusion

We have seen that the symmetry principles manifest themselves distinctly in the structure of biomolecules and their associations. Despite the initial asymmetry of small protomolecules, either the exact symmetry or pseudosymmetry stands out at further levels of organization in the primary, secondary and quaternary structure. Symmetry in biostructures may be explained in terms of expediency of their mechanism for fulfilling some or other functions, this expediency has been elaborated by the evolutionary process. The general physical principles enabling the symmetry to manifest itself are performed by the genetically determined frameworks of biological processes.

Symmetry of macroorganisms obeys their interaction with the environment. The Earth's gravitational force in combination with the necessity of moving forward defines not only the morphological symmetry m of the majority of the organisms living on the Earth, but also the symmetry of propulsion devices created by a human—bicycle, airplane etc. Plants and animals living in the Ocean, that do not move on their own, are often found to possess the axial symmetry.

REFERENCES

1. A. V. Shubnikov and V. A. Koptsik, *Symmetry in Science and Art*. Plenum Press, New York (1974).
2. H. Weyl, *Symmetry*. Princeton University Press, Princeton, New Jersey (1952).
3. B. K. Vainshtein, *Modern Crystallography. I. Symmetry of Crystals, Methods of Structural Crystallography*, Springer Series in Solid-State Sciences, Vol. 15. Springer-Verlag, Berlin, Heidelberg, New York (1981).
4. E. Schrödinger, *What is Life? The Physical Aspects of the Living Cell*. The University Press, Cambridge (1945).
5. J. D. Bernal, *The Origin of Life*. Weidenfeld and Nicolson, London (1967).
6. B. K. Vainshtein, *Diffraction of X-rays by Chain Molecule*. Amsterdam, London, New York (1966).
7. T. L. Blundell and L. N. Johnson, *Protein Crystallography*. Academic Press, New York (1976).
8. N. E. Zhukhlistova and G. N. Tishchenko, Kristallicheskaya struktura Na, Ni-kompleksa enniatina B. *Kristallografiya* **26**, 1232–1239 (1981).
9. L. Pauling and R. B. Corey, H. R. Branson, The structure of proteins: two hydrogen-bonded helical configurations of the polypeptide chain, *Proc. Nat. Acad. Sci.* **37**, pp. 205–211 (1951).
10. F. H. C. Crick and J. D. Watson, The complementary structure of deoxyribonucleic acid. *Proc. Roy. Soc., London* **A223**, 80–96 (1954).
11. G. H. Ramachandran and G. Kartha, Structure of collagen. *Nature, London*. **176**, 593–595 (1955).
12. E. G. Harutyunyan, Struktura Leggemoglobina, *Molekulyarnaya Biologiya* **15**, 27–44 (1981).
13. M. Levitt and C. Chothia, Structural patterns in globular proteins. *Nature, London* **261**, 552–558 (1976).
14. J. S. Richardson, β-sheet topology and the relatedness of proteins. *Nature, London* **268**, 495–500 (1977); The anatomy and taxonomy of protein structure. *Adv. Protein Chemistry* **34**, 167–339 (1981).
15. H. C. Watson and J. C. Kendrew, The stereochemistry of the protein myoglobin. *Prog. Stereochem.* **4**, 299–321 (1969).
16. W. A. Hendrickson and K. B. Ward, Pseudosymmetry in the structure of myohemerythrin. *J. Biol. Chem.* **252**, 3012–3018 (1977).
17. Yu. N. Chirgadze, Yu. V. Sergeyev, N. P. Fomenkova, V. D. Oreshin and S. V. Nikonov, Struktura γ-kristallina IIIb iz glaznoy linzy telenka pri razreshenii 3 Å. *Dokl. AN SSSR* **259**, 1502–1505 (1981).
18. F. A. Quiocho and W. N. Lipscomb, Carboxypeptidase A: A protein and an enzyme. *Adv. Protein Chem.* **25**, 1–78 (1971).
19. B. K. Vainshtein, W. R. Melik-Adamyan, V. V. Barynin, A. A. Vagin and A. I. Grebenko, Three-dimensional structure of the enzyme catalase. *Nature, London* **293**, 411–412 (1981).
20. V. V. Borisov, S. N. Borisova, N. I. Sosfenov, A. A. Vagin, Yu. V. Nekrasov, B. K. Vainshtein, V. M. Kochkina and A. E. Braunshtein, Prostranstvennyi khod polipeptidnoy tsepi v molekule aspartat-transaminazy. *Dokl. AN SSSR* **250**, 988–991 (1980).
21. M. F. Perutz, Structure and function of haemoglobin. I. A tentative atomic model of horse oxyhaemoglobin. *J. Mol. Biol.* **13**, 646–668 (1965).
22. M. Levine, H. Muirhead, D. K. Stammers and D. I. Stuart, Structure of pyruvate kinase and similarities with other enzymes: possible implications for protein taxonomy and evolution. *Nature, London* **271**, 626–630 (1978).
23. A. V. Crewe, D. A. Crewe and O. H. Kapp, Inexact three-dimensional reconstruction of a biological macromolecule from a restricted number of projections. *Ultramicroscopy* **13**, 365–372 (1984).
24. D. L. D. Caspar and A. Klug, Physical principles in the construction of regular viruses. *Cold Spring Harbor Symp. Quant. Biol.* **27**, 1–24 (1962).

25. S. C. Harrison, A. J. Olson, C. E. Schutt, F. K. Winkler and G. Bricogne, Tomato bushy stunt virus at 2.9 Å resolution. *Nature, London* **276**, 368–373 (1978).
26. I. Rayment, T. S. Baker, D. L. D. Caspar and W. T. Murakami, Polyoma virus capsid structure at 22.5 Å resolution. *Nature, London* **295**, 110–115 (1982).
27. B. K. Vainshtein, Tubular crystals of globular proteins, *Mat. Res. Bull.* **7**, 1347–1356 (1972).
28. I. Ohtsuki. Localization of troponin in thin filament and tropomyosin paracrystal. *J. Biochem.* **75**, 753–763 (1974).
29. A. Klug and D. L. D. Caspar, The structure of small viruses. *Adv. Virus Res.* **7**, 225–325 (1960).
30. A. C. H. Durham, J. T. Finch and A. Klug, States of aggregation of tobacco mosaic virus protein. *Nature, London* **229**, 37–50 (1971).
31. B. K. Vainshtein, A. M. Mikhailov, A. S. Kaftanova, M. Platzer and I. A. Andriashvili, Electron microscopic studies of spatial structure of phage Fi-I, Electron Microscopy 1980, v.2. Biology, Proc. 7-th European Congress on Electron Microscopy, Netherlands, 600–601 (1980).
32. B. K. Vainshtein, N. A. Kiselev and V. L. Spitzberg, Kristallizatsiya katalazy v truby s monomolekulyarnymi stenkami. *Dokl. AN ASSR* **167**, 211–214 (1966).
33. N. A. Kiselev, F. Ya. Lerner, and N. B. Livanova, Electron microscopy of muscle phosphorylase a. *J. Mol. Biol.* **86**, 587–599, (1974).
34. V. V. Barynin, B. K. Vainshtein, O. N. Zograf and S. Ya. Karpukhina, Trekhmernaya rekonstruktsiya trubchatykh kristallov katalazy. *Molekulyarnaya Biologiya* **13**, 1189–1197 (1979).
35. L. K. Tamm, R. H. Crepau and S. J. Edelstein, Three-dimensional reconstruction of tubulin in zinc-induced sheets, *J. Mol. Biol.* **130**, 473–492 (1979).
36. B. K. Vainshtein, V. M. Fridkin and V. L. Indenbom, *Modern Crystallography. II. Structure of Crystals*, Springer Series in Solid-State Sciences, vol. 21. Springer-Verlag, Berlin, Heidelberg, New York (1982).
37. R. E. Dickerson, H. R. Drew, B. N. Conner, R. M. Wing, A. V. Fratini and M. L. Kopka, The anatomy of A-, B-, and Z-DNA. *Science* **216**, 475–485 (1982).
38. Z. Shakked, D. Rabinovich, W. B. T. Cruse, E. Egert, O. Kennard, G. Sala, S. A. Salisbury and M. A. Viswamitra, Crystalline A-DNA: the X-ray analysis of the fragment d(G-G-T-A-T-A-C-C). *Proc. Roy. Soc. London* **B213**, 479–489 (1981).
39. A. H.-J. Wang, G. J. Quigley, F. J. Kolpak, J. L. Crawford, J. H. von Boom, C. van der Mazel and A. Rich, Molecular structure of a left-handed double helical DNA fragment at atomic resolution. *Nature, London* **282**, 680–686 (1979).
40. S. H. Kim, F. L. Suddath, G. J. Quigley, A. McPherson, J. L. Sussman, A. H.-J. Wang, N. C. Seeman and A. Rich, Three-dimensional tertiary structure of yeast phenylalanine transfer RNA. *Science* **185**, 435–440 (1974).
41. J. T. Finch, L. C. Lutter, D. Rhodes, R. S. Brown, B. Rushton, M. Levitt and A. Klug, Structure of nucleosome core particles of chromatin. *Nature, London* **269**, 29–36 (1977).
42. D. Hodgkin, Mgnoveniya otkrytii. *Kristallografiya* **26**, 1029–1045 (1981).
43. A. I. Kitaigorodsky, *Organic Chemistry and Crystallography*. Consultants Bureau, New York (1961).
44. V. A. Koptsik, Printsipy simmetrizatsii-dissimetrizatsii Shubnikova-Curie dlya sostavnykh fizicheskikh sistem, in: *Problemy sovremennoy kristallograffi* p. 42–61. Nauka, Moskva (1975).